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(54) **Title**: PHENYL-ISOXAZOL DERIVATIVES AND PREPARATION PROCESS THEREOF

(57) **Abstract**: Disclosed are a phenyl-isoxazol derivative compound, which is useful as a treatment material for virus infection, especially, infection of an influenza virus, or its pharmaceutically acceptable derivative, a preparation method thereof, and an illness treatment pharmaceutical composition including the compound as an active ingredient.

Description

Title of Invention: PHENYL-ISOXAZOL DERIVATIVES AND PREPARATION PROCESS THEREOF

Technical Field

[1] The present invention relates to a novel phenyl-isoxazol derivative having antiviral activity against an influenza virus and other similar viruses, which is useful in treatment and prevention of virus infection. Also, the present invention relates to a method using a compound for treating or preventing infection of an influenza virus and other similar viruses, a composition including the compound, a preparation method of the compound, and a synthesis intermediate used for the preparation method.

[2]

Background Art

[3] An influenza virus causes infectious acute febrile respiratory illness in a host. When the influenza virus is epidemic, it can easily spread across borders due to its strong infectiousness. Also, it may be unpredictably variously mutated, thereby causing interspecific infection. Thus, it is necessary to provide worldwide common countermeasures and monitoring systems.

[4] An influenza virus is taxonomically defined as a member of Orthomyxovirus, and has three types of A, B, and C. Especially, A, and Btypes are epidemically spread. Type A influenza has a high mutatability, and zoonotically infects birds, pigs, and horses, as well as humans. Furthermore, the type A influenza includes various subtypes according to a combination of surface antigens (HA and NA). Unlike type A influenza, type B influenza causes relatively light symptoms, and infects humans and seals. Especially, in humans, it mainly causes an illness in children. Type C influenza can infect humans and pigs, but is known to have relatively low pathogenicity to humans. On the surface of these viruses, two kinds of surface antigens (that is, glycoproteins of Hemagglutinin (HA) and Neuraminidase (NA)) exist. Also, within the viruses, 8 fragmented RNAs exist. Hemagglutinin has a trimer structure including a head and a stem. The head region is related to most antigen mutations, which attaches the virus to a host cell by binding to a terminal sialic acid residue on the surface of the host cell, and sequentially allows the virus to penetrate the host cell. Neuraminidase is a mushroom-shaped tetramer with a head and a stem. On the surface of the head, an active region exists, which cleaves the alpha-ketosidic bond linking a terminal neuraminic acid residue to the oligosaccharide moiety on the cell surface. This cleavage performs an important role when a replicated and propagated virus within the infected cell comes out from the host cell and penetrates a respiratory organ mucous

membrane cell. Surface antigens of a virus are mutated in the same subtype, and a new antigen mutant strain appears annually. Especially, from among influenza viruses, an avian influenza virus that has been problematic recently, infects various kinds of birds such as chickens, turkeys, ducks and wild birds through antigenic shift and quickly spreads. When chickens are infected with the virus, the morality rate is 80% or more. Thus, it is a virus causing serious damage and threatening the poultry farming industry worldwide. Further, it is reported that its ripple effect is not limited to the poultry farming industry. In other words, the virus may spread to humans by infecting a human body. Accordingly, research on the treatment of a virus may include inhibition of adsorption into an epithelial cell, inhibition of penetration into a cell, inhibition of transcription and replication of a gene, inhibition of protein synthesis, inhibition of release from a cell, and the like. Each of these is an objective of development of a novel antiviral drug.

[5]

[6] Table 0

[Table 0]

FIG. 1. Amantadine	FIG. 2. Rimantadine

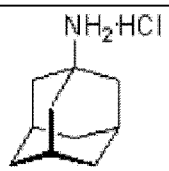
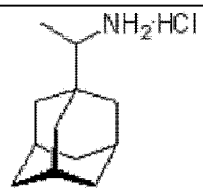
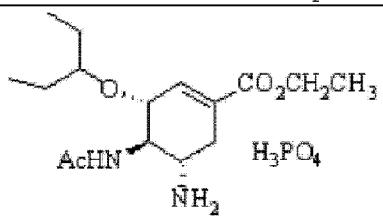
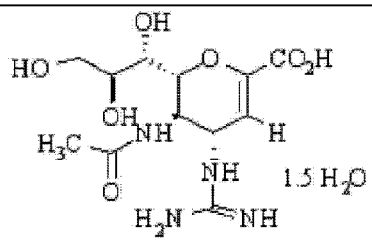

	

FIG. 3. Oseltamivir Phosphate	FIG. 4. Zanamivir
	

[7]

[8] Conventionally developed representative therapeutic agents for treating an influenza virus include 4 materials such as Amantadine, Rimantadine, Zanamivir, and Oseltamivir, which were approved by the US Food and Drug Administration (FDA) (see FIGs. 1 to 4). Amantadine or Rimantadine is an M2 ion channel blocker having activity only against a Hamagglutinin virus strain (an influenza virus), and interrupts replication of a virus particle introduced into a host cell. These drugs are effective in only type A influenza virus A. Also, since they have been used for 40 years, it is known that a virus resistant to the drugs has been generated, and the drugs cause serious side effects in a nervous system and a stomach. Meanwhile, Oseltamivir

(Korean Patent Publication No. 10-1998-0703600) or Zanamivir (Korean Registered Patent 0169496) is a Neuraminidase inhibitor having activity only against a Neuraminidase virus strain (influenza virus) and interrupts a replicated virus from escaping from a host cell. The two kinds of therapeutic agents intervene in one process of influenza virus infection and interrupt the process, thereby inhibiting of the propagation of a virus. However, Zanamivir has a high antiviral effect, but has disadvantages such as a low bioavailability and a quick release from a kidney. Also, in Oseltamivir, there have been reported some side effects such as generation of a resistant virus, and serious emesis symptoms.

[9] Following these drugs used as antiviral therapeutic agents, mutant viruses having serious side effects, tolerance, and strong resistance have rapidly appeared recently. Thus, their application requires great care. Also, in the development of a vaccine, there is a problem in that when an epidemic virus type does not correspond to a virus of the vaccine, the effect is insignificant. Accordingly, it is highly required to develop an improved drug that has a high effect in treatment and prevention of influenza infection, and has a high stability.

[10]

Disclosure of Invention

Technical Problem

[11] Through research, the inventors of the present invention invented, as a better antiviral agent than a conventional agent, a novel phenyl-isoxazol compound having a high influenza virus inhibiting activity, and a high preventive effect of virus replication, which can treat or prevent an illness caused by an influenza virus.

[12] The present invention has been made to solve the above mentioned disadvantages. As a result, the inventors found a compound represented by Formula 1, which has a different novel structure from a conventionally developed compound structure. Then, based on the finding, they completed this invention.

[13]

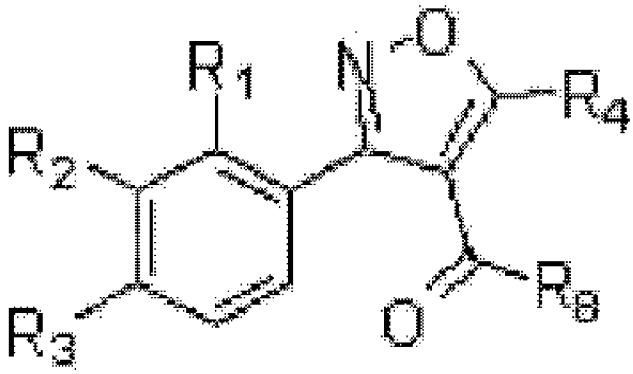
Solution to Problem

[14] In accordance with an aspect of the present invention, there is provided a phenyl-isoxazol derivative represented by Formula 1 below, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite.

[15]

[16] Formula 1

[17]



[18] In Formula above,

[19] R_1, R_2 and R_3 each independently represents hydrogen, lower alkyl optionally substituted with halogen, lower alkoxy optionally substituted with halogen, or halogen,

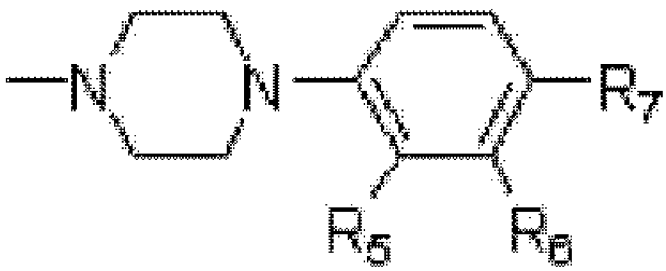
[20] R_4 represents methyl or amine, and

[21] R_8 may be substituted with a radical of Formula 2 below, or substituted with a radical of Formula 3 below,

[22]

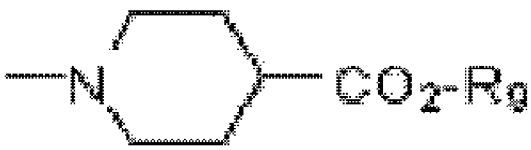
[23] Formula 2

[24]



[25] Formula 3

[26]



[27] wherein, R_5, R_6 and R_7 each independently represents hydrogen, lower alkyl optionally substituted with halogen, hydroxy, lower alkoxy or halogen, and

[28] R_9 represents lower alkyl.

[29] In accordance with another aspect of the present invention, there is provided a composition including the inventive compound, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, and a pharmaceutically acceptable carrier or excipient.

[30] In accordance with a further aspect of the present invention, there is provided a pharmaceutical composition for treating or preventing virus infection, the composition

includes the inventive compound, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, and a pharmaceutically acceptable carrier or excipient.

[31] In accordance with a still further aspect of the present invention, there is provided the use of the preventive compound, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, for preparing a pharmaceutical composition for treatment or prevention of virus infection.

[32] In accordance with a still yet further aspect of the present invention, there is provided a method for preventing or treating virus infection, the method including the step of administering a therapeuticallyeffective amount of the inventive compound, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, to mammals, including humans, requiring virus infection treatment or prevention.

[33]

Mode for the Invention

[34] Hereinafter, the present invention will be described in detail.

[35] An influenza virus infection caused by an influenza virus is an illness frequently lethal to humans and animals. The influenza virus causes an infectious acute febrile respiratory organ illness in a host. When the influenza virus is epidemic, it can easily spread across borders due to its strong infectiousness. Also, it may be unpredictably variously mutated, thereby causinginterspecific infection. Thus, it is necessary to provide worldwide common countermeasures and monitoring systems.

[36] However, unlike an antifungal agent, etc. there exist only limited kinds of drugs applicable to influenza. For example, at present, representative therapeutic agents that have been recently used as Neuraminidase inhibitors include Oseltamivir and Zanamivir. These therapeutic agents perform a role of inhibiting the propagation of an influenza virus. However, Zanamivir has a high antiviral effect but has disadvantages such as a low bioavailability and a quick release from a kidney. Also, in Oseltamivir, there have been reported some side effects such as generation of a resistant virus, and serious emesis symptoms.

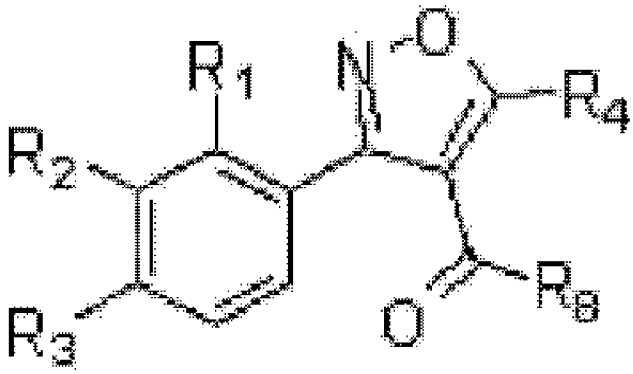
[37] The inventors of the present invention found a compound represented by Formula 1 below, that is, a phenyl-isoxazol derivative, which has a higher antiviral activity against an influenza virus, and a higher susceptibility to a virus replication inhibitor inhibiting virus replication than its corresponding Oseltamivir phosphate.

[38] Accordingly, the present invention provides a compound represented by Formula 1 below, and its pharmaceutically acceptable derivative.

[39]

[40] Formula 1

[41]



[42]

[43] In Formula 1, R_1, R_2, R_3, R_4 and R_8 are the same as defined above.

[44]

[45] In the present invention, it is understood that "a compound represented by Formula 1" (or "the inventive compound"), as long as not explicitly stated otherwise, includes its hydrate, solvate, pharmaceutically acceptable salt, prodrug, composite, and pharmaceutically acceptable derivative including diastereomer or enantiomer.

[46] In the present invention, the term "lower alkyl" indicates a straight-chain or branched saturated aliphatic hydrocarbon radical that preferably includes 1 to 12 carbon atoms, alternatively 1 to 8 carbon atoms, or alternatively 1 to 6 carbon atoms. Examples of thealkyl radical may include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secondary-butyl, tertiary-butyl, pentyl, isoamyl, n-hexyl, and the like, but the present invention is not limited thereto. In the present invention, an alkyl group may be optionally substituted.

[47] Also, the term "alkoxy" indicates oxygen added with an alkyl substituent. In the present invention, an alkoxy group may be optionally substituted.

[48] Also, the term "lower halo alkyl" indicates a straight-chain or branched saturated aliphatic radical that preferably includes 1 to 12 carbon atoms, alternatively 1 to 8 carbon atoms, or alternatively 1 to 6 carbon atoms, in which hydrogen is substituted with halogen.

[49] Also, the term "halogen" indicates an atom of fluoro, chlorine, bromine or iodine, and preferably indicates fluoro or chlorine. In the present invention, a halogen group may be optionally substituted.

[50] The inventive compound also includes a salt within the scope of the present invention. It is understood that the inventive compound, e.g., the compound represented by Formula 1, as long as not explicitly stated otherwise, includes its salt.

[51] In this specification, the term "salt" indicates an acidic and/or basic salt formed from inorganic and/or organic acid and base. The salt of the inventive compound may be, for example, formed by reacting the inventive compound with an acid or a base in the

same amount as that of the compound in a medium or aqueous medium capable of precipitating the salt.

[52] Non-limiting examples of the salt may include the following salts. The compound may be reacted with acetic acid, adipic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphorsulfonic acid, citric acid, cyclamate, ethane-1,2-disulphonic acid, ethanesulfonic acid, 2-hydroxy ethanesulfonic acid, formic acid, fumaric acid, bromic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, malic acid, maleic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthalate, nicotinic acid, trifluoroacetic acid, oxalic acid, p-toluene sulfonic acid, propionic acid, glycolic acid, succinic acid, tartaric acid, oxalic acid, amino acid (e.g., lysin), salicylic acid, 2,2-chloroacetic acid, L-aspartic acid, (+)-(1S)-camphor-10-sulfonic acid, 4-acetamido benzoic acid, caproic acid, cinnamic acid, gentistic acid, glutaric acid, malonic acid, mandelic acid, ortic acid, pamoate, aminosalicylic acid or the like to form an acid addition salt. When a lot of basic groups exist, a mono or poly acid addition salt may be formed.

[53] Also, the compound represented by Formula 1 has ethylester as a functional group, and thus may form a carboxyl group. Under an acidic or basic condition, for example, at pH 11-12 (with a base such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, or ammonium hydroxide) or at pH 2-3 (with an acid such as hydrochloric acid or sulfuric acid), ethylester of the compound represented by Formula 1may be hydrolyzed. The hydrolyzedcompound represented by Formula 1 includes a carboxyl group, thereby forming a cation and a salt. There is no specific limitation in the kind of such a salt, as long as it is pharmaceutically acceptable. Examples of such a salt may include an alkaline metal salt, such as sodium, potassium and lithium salt an alkaline earth metal salt, such as calcium and magnesium salt other metal salts, such as aluminum, iron, zinc, copper nickel, and cobalt salt other inorganic salts, such as ammonium salt an amine salt, such as t-octylamine, dibenzylamine, morpholin, glucosamine, phenylglycine alkyl ester, ethylenediamine, methylglucamine, guanidine, diethylamine, triethylamine, dicyclohexylamine, N,N-dibenzylethylenediamine, chloroprocaine, procaine, diethaneolamine, benzylphenethylamine, piperazine, tetraethylammonium and tris(hydroxymethyl)aminomethane salt.

[54] In this specification, the term "pharmaceutically acceptable derivative" indicates the inventive compounds hydrate, solvate, pharmaceutically acceptable salt, prodrug, or composite, which maintains the required biological activity of the compound and does not show an unwanted toxicological effect.

[55] The present invention also includes a prodrug of the inventive compound. The term "prodrug" indicates a compound covalently bonded to a carrier. The prodrug may

release an active ingredient while being administered to a mammal subject. The release of the active ingredient may occur within a living body,and the prodrug may be prepared by technologies known to a person skilled in the art. In such technologies, in a certain compound, an appropriate functional group is modified. However, the modified functional group regenerates an original functional group through a general operation or within a living body. Non-limiting examples of the prodrug include ester (e.g., acetate, formate, and benzoate derivative) and the like.

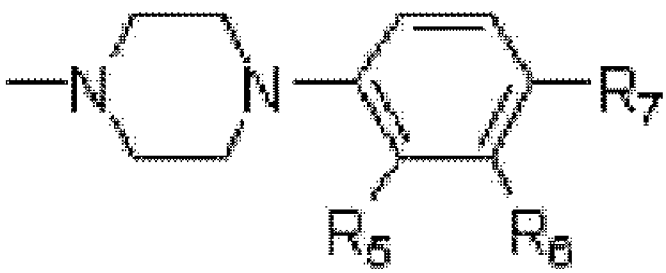
[56] The inventive compound has an inhibiting activity against a strain of an influenza virus, and is highly effective in the treatment and the prevention of infection of influenza having susceptibility to a virus replication inhibitorinhibiting virus replication, and other similar viruses.

[57] According to an embodiment of the present invention, in the compound represented by Formula 1, preferably, when the radical in Formula 2 is substituted for R_8, two from among R_1, R_2 and R_3 represent hydrogen, the remaining one represents lower alkyl optionally substituted with halogen, lower alkoxy optionally substituted with halogen, or halogen, preferably fluoro or chlorine. R_4 represents methyl, or amine, and from among R_5, R_6 and R_7, one or two each independently represents hydrogen, lower alkyl optionally substituted with halogen, hydroxy, lower alkoxy, or halogen or R_1 represents halogen, preferably chlorine, R_4 represents methyl or amine, R_2, R_3, R_5, and R_7 each represents hydrogen, and R_6 represents alkoxy, preferably methoxy. When the radical in Formula 3 is substituted for R_8, two from among R_1, R_2 and R_3 represent hydrogen, the remaining one represents lower alkyl optionally substituted with halogen, lower alkoxy optionally substituted with halogen, or halogen, R_4 represents amine, and R_9 represents lower alkyl.

[58]

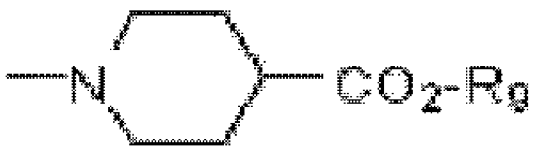
[59] Formula 2

[60]



[61] Formula 3

[62]



[63]

[64] In another embodiment of the present invention, in the compound represented by Formula 1, more preferably, when the radical of Formula 2 is substituted for R_8, two from among R_1, R_2 and R_3 represent hydrogen, the other one represents trifluoromethyl, fluoro, or trifluoromethoxy, R_4 represents methyl or amine, from among R_5, R_6 and R_7, one or two each independently represents hydrogen, methoxy, chlorine, fluoro, trifluoromethyl or hydroxy; or R_1 represents halogen, preferably chlorine, R_4 represents methyl or amine, R_2, R_3, R_5, and R_7 each represents hydrogen, and R_6 represents alkoxy, preferably methoxy. When the radical of Formula 3 is substituted for R_8, R_4 represents amine, two from among R_1, R_2 and R_3 represent hydrogen, the remaining one represents trifluoromethyl, fluoro, or trifluoromethoxy, and R_9 represents methyl or ethyl. In view of inhibition of influenza virus, especially, when the radical of Formula 2 is substituted for R_8, R_1 represents trifluoromethyl, or trifluoromethoxy, R_2 and R_3 represent hydrogen, R_4 represents methyl, and from among R_5, R_6 and R_7, one or two each independently represents hydrogen, hydroxy, methoxy, or chlorine R_1 represents chlorine, R_4 represents methyl, R_2, R_3, R_5 and R_7 represent hydrogen, and R_6 represents methoxy or R_2 represents fluoro, trifluoromethyl, or trifluoromethoxy, R_1 and R_3 represent hydrogen, R_4 represents methyl or amine, and from among R_5, R_6 andR_7, one or two each independently represents hydrogen, hydroxy, methoxy, trifluoromethyl or chlorine. Meanwhile, when the radical of Formula 3 is substituted for R_8, R_1 represents trifluoromethoxy, R_2 and R_3 represent hydrogen, R_4 represents amine, and R_9 represents ethyl.

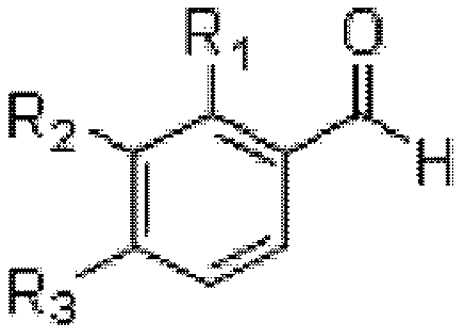
[65] The inventive compound represented by Formula 1 may be prepared by the following synthesis process. The isomer and solvate (e.g., hydrate) of the compound represented by Formula 1 are also within the scope of the present invention. The solvation method is generally known in the art. Accordingly, the inventive compound may be used in the form of a pharmaceutically useful hydrate or salt, and obtained by the method described by Reaction Scheme below.

[66] The inventive compound of Formula 1 is prepared by the steps of: reacting a compound represented by Formula 4 below preferably with hydroxylammonium-chloride in the presence of a base to produce a compound represented by Formula 5 below chlorinating the compound represented by Formula 5 so as to produce a compound represented by Formula 6 below cyclizing the compound represented by Formula 6 so as to produce a compound represented by Formula 7 below as an isoxazol compound removing R_{10} as a protecting group of Formula 7 so as to produce a compound represented by Formula 8 and reacting the compound represented by Formula 8 with a compound represented by Formula 2 or Formula 3 so as to produce a compound represented by Formula 9a or Formula 9b.

[67]

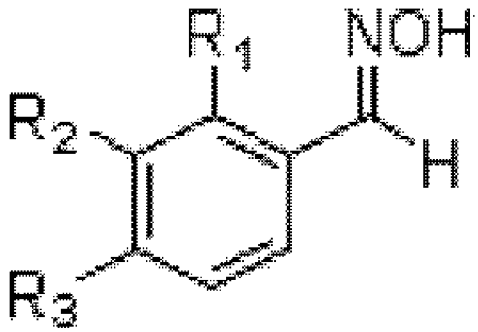
[68] Formula 4

[69]



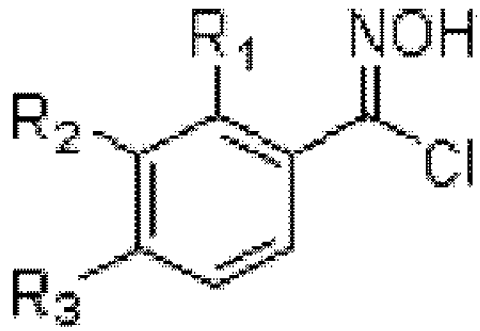
[70] Formula 5

[71]



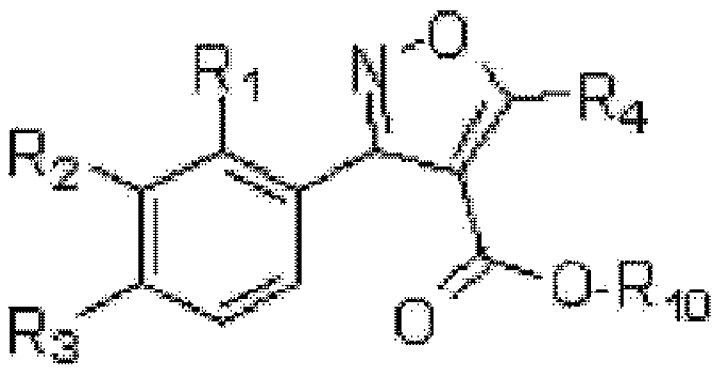
[72] Formula 6

[73]



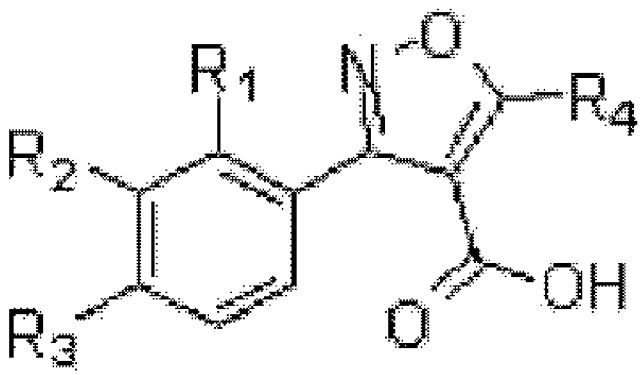
[74] Formula 7

[75]



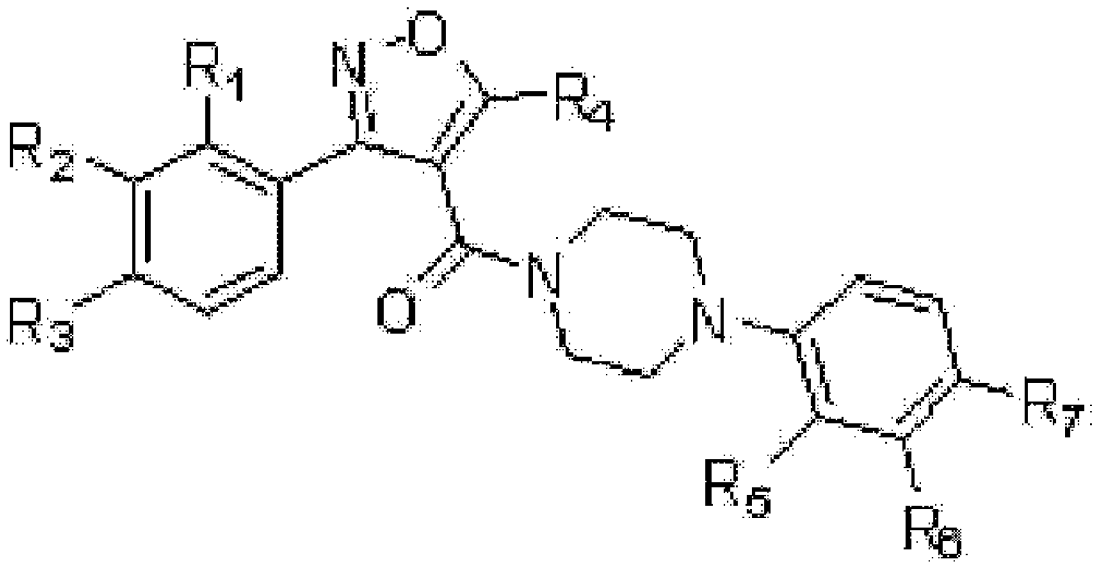
[76] Formula 8

[77]



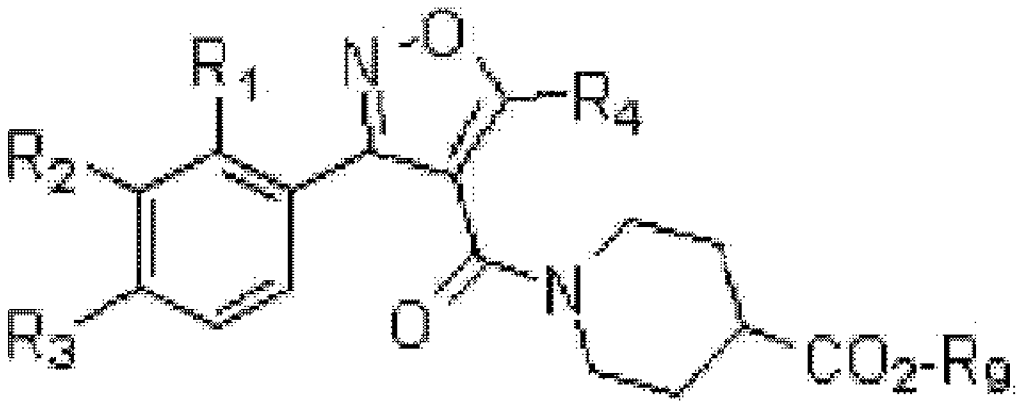
[78] Formula 9a

[79]



[80] Formula 9b

[81]



[82] In Formulas above,

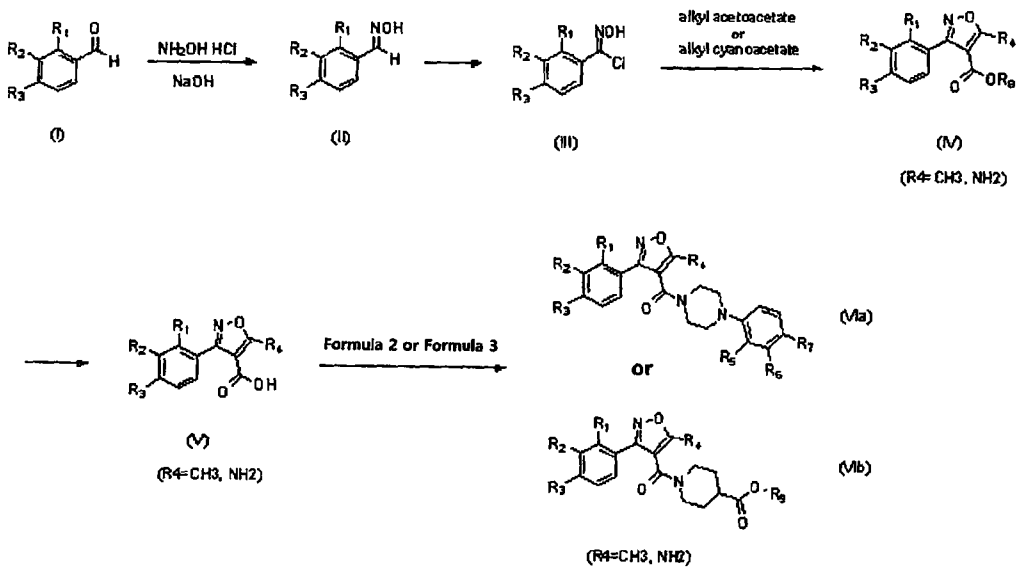
[83] R_1 to R_9 are the same as defined above, and

[84] R_{10} represents lower alkyl, preferably methyl, ethyl or isopropyl group.

[85]

[86] Reaction scheme 1

[87]



[88] In Reaction scheme 1 above, R_1 to R_{10} are the same as defined above.

[89] A phenylaldehyde compound (I) having R_1, R_2 and R_3 substituted onto a benzene ring was commercially available. The phenylaldehyde compound (I) is reacted with hydroxylammoniumchloride or its equivalent in the presence of a base so as to synthesize a compound of benzaldehyde oxime (II). Then, through a chlorination reaction, a benzimidoyl chloride compound (III) is produced. An isoxazol compound (V) in which R_4 is substituted with methyl or amine may be obtained through a generally used synthesis method (cyclization reaction) by using alkyl acetoacetate or alkyl cyanoacetate. From a phenyl-isoxazol derivative compound (V, R_4=methyl) or a compound (V, R_4=amine) including a carboxyl group and an amine group, a phenyl-isoxazol derivative compound (VIa or VIb) is produced by using 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimidehydrochloride (EDCl) or hydroxybenzotriazol (HOBt) in the presence of a base.

[90] The inventive preparation method may be carried out preferably in a solvent in the presence of a base or an acid. Herein, there is no specific limitation in a solvent, an acid, and a baseas long as they have no adverse effect on the reaction. For example, the solvent may be at least one kind selected from the group consisting of tetrahydrofuran, methylenechloride, ethanol, N,N-dimethylformamide, N,N-dimethylacetamide, ethylacetate, tert-butanol, toluene, and dioxane. The base may be at least one kind selected from the group consisting of pyridine, triethylamine, diethylamine, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, lithium aluminum hydride, lithium borohydride, and sodium nitrate, and cesium carbonate. The acid may be at least one kind selected from the group consisting of tri-

fluoroacetic acid, hydrochloric acid, nitric acid, sulfuric acid, bromic acid, and acetic acid.

[91] Starting materialsused in the preparation of the inventive compounds according to the method are commercially available, or can be easily bought. The reaction may be generally carried out under a cooling or heating condition. After the reaction, through a general after-treatment process, such as column chromatography, recrystallization, etc. a final compound may be purified.

[92] Meanwhile, the present inventionis related to a pharmaceutical compositionfor treating or preventing virus infection, in which the compound represented by Formula 1, or its pharmaceutically acceptable derivative is administered in an effective amount to mammals, including humans. Especially, the composition is effective in inhibiting influenza infection, and thus may be effectively used in the treatment of such an illness.

[93] When the inventive compounds determined to be effective in inhibiting the illness is administered, a single dose or a multiple dose generally ranges from 0.01 to 750mg/kg per day, preferably ranges from 0.1 to 100mg, and most preferably ranges from 0.5 to 25mg. However, the specific dose for an individual patient may vary according to a specific compound, a patient's weight, sex, diet, a drug administration time, an administration method, a release ratio, a drug mixing ratio, a patient's state, age, etc.

[94] The inventive compound may be administered without being processed in the treatment. However, the active ingredient is preferably provided as a pharmaceutical formulation.

[95] Accordingly, the present invention provides a pharmaceutical formulation obtained by mixing a compound represented by Formula 1 or its pharmaceutically acceptable derivative with a pharmaceutically acceptable carrier and/or excipient.

[96] Also, the inventive compoundmay be administered via any suitable route. However, preferably, the compound is administered by injection or in oral form.

[97] An injection preparation, for example, a sterile injection aqueous or oily suspension, may be prepared by using an appropriate material such as a dispersant, a wetting agent or a suspension according to a known art. As a solvent, water, ringer's solution or isotonic NaCl solution may be used. Also, sterile fixed oil is also generally used as a solvent or a suspension medium. For this, any nonirritating fixed oil, including monoglyceride or di-glyceride, may be used. Also, fatty acid such as oleic acid may used in injection preparation.

[98] A solid administration form for oral administration may include capsule, tablet, pill, powder and granule forms. Especially, capsule and tablet forms are preferred. Preferably, tablet and pill forms are prepared as intestinal drugs. The solid administration form may be prepared by mixing the inventive active compound represented

by Formula 1 with at least one inert diluent (such as sucrose, lactose, starch), a lubricant (such as magnesium stearate), and a carrier (such as a disintegrating agent, a binding agent, etc.).

[99] The inventive compound has an inhibiting activity against a strain of an influenza virus, and may be used to treat and prevent infection of influenza having susceptibility to a Neuraminidase inhibitor or a virus replication inhibitor inhibiting virus replication, and other similar viruses. Herein, it may be used in combination with a secondary therapeutic agent having an activity against the same virus. This compound, for example, may be used in combination with Zanamivir, Oseltamivir, Amantadine, Rimantadine or the like. The administration amount of each compound may be the same or different, compared to the administration amount of the compound alone.

[100] Hereinafter, the present invention will be described in more detail with reference to Preparation Examples and Examples. However, Preparation Examples and Examples, as described below, are illustrative only, and do not limit the present invention.

[101]

[102] Preparation Example 1

[103] synthesis of 2-(trifluoromethyl)benzaldehydeoxime

[104] 2-(trifluoromethyl)benzaldehyde (34.82g, 200.0mmol) was dissolved in ethanol (200mL), and added with sodium hydroxide (12.00g, 300.0mmol) dissolved in purified water (50mL). Hydrochloric acidhydroxylamine (16.68g, 240mmol) dissolved in purified water (50mL) was added thereto, followed by stirring for 3 hours. After the reaction was completed, the resultant product was added with ice. The produced solid was filtered, washed with purified water (600mL), and dried so as to provide a white solid required compound (32.15g, 171mmol, 85%).

[105] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.23 (dd, 1H), 7.59 (dd, 1H), 7.76 (m, 2H), 8.39 (s, 1H), 11.63 (s, 1H)

[106]

[107] Preparation Example 2

[108] synthesis of 2-chlorobenzaldehydeoxime

[109] In a similar manner as described in Preparation Example 1, by using 2-chlorobenzaldehyde (29.14g, 200.0mmol), sodium hydroxide (12.00g, 300.0mmol) and hydrochloric acidhydroxylamine (16.68g, 240mmol), a white solid required compound (29.73g, 189mmol, 95%)was obtained.

[110] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.37 (m, 2H), 7.48 (dd, 1H), 7.82 (dd, 1H), 8.37 (s, 1H), 11.28 (s, 1H)

[111]

[112] Preparation Example 3

[113] synthesis of 3-fluorobenzaldehydeoxime

[114] In a similar manner as described in Preparation Example 1, by using 3-fluorobenzaldehyde (24.82g, 200.0mmol), sodium hydroxide (12.00g, 300.0mmol) and hydrochloric acidhydroxylamine (16.68g, 240mmol), a white solid required compound (22.48g, 162mmol, 81%) was obtained.

[115] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.32 (m, 1H), 7.56 (m, 3H), 8.20 (s, 1H)

[116]

[117] Preparation Example 4

[118] synthesis of 2-fluorobenzaldehydeoxime

[119] In a similar manner as described in Preparation Example 1, by using 2-fluorobenzaldehyde (24.82g, 200.0mmol), sodium hydroxide (12.00g, 300.0mmol) and hydrochloric acidhydroxylamine (16.68g, 240mmol), a white solid required compound(25.96g, 186mmol, 93%) was obtained.

[120] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.22 (m, 1H), 7.45 (m, 1H), 7.65 (m, 2H), 8.15 (s, 1H)

[121]

[122] Preparation Example 5

[123] synthesis of 4-(trifluoromethoxy)benzaldehydeoxime

[124] In a similar manner as described in Preparation Example 1, by using 4-(trifluoromethoxy)benzaldehyde (38.02g, 200.0mmol), sodium hydroxide (12.00g, 300.0mmol) and hydrochloric acidhydroxylamine (16.68g, 240mmol), a white solid required compound(38.68g, 188mmol, 94%) was obtained.

[125] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.38 (d, 2H), 7.72 (tt, 2H), 8.20 (s, 1H), 11.43 (s, 1H)

[126]

[127] Preparation Example 6

[128] synthesis of 2-(trifluoromethoxy)benzaldehydeoxime

[129] In a similar manner as described in Preparation Example 1, by using 2-(trifluoromethoxy)benzaldehyde (38.03g, 200.0mmol), sodium hydroxide (12.00g, 300.0mmol) and hydrochloric acidhydroxylamine (16.6g, 240mmol), a white solid required compound(38.67g, 188mmol, 94%) was obtained.

[130] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.43 (m, 2H), 7.54 (m, 1H), 7.89 (m, 1H), 8.24 (s, 1H), 11.76 (s, 1H)

[131]

[132] Preparation Example 7

[133] synthesis of 3-(trifluoromethyl)benzaldehydeoxime

[134] In a similar manner as described in Preparation Example 1, by using 3-(trifluoromethyl)benzaldehyde (34.82g, 200.0mmol), sodium hydroxide (12.00g, 300.0mmol) and hydrochloric acidhydroxylamine (16.68g, 240mmol), a white solid required compound(35.33g, 187mmol, 93%) was obtained.

[135] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.33 (m, 1H), 7.72 (m, 3H), 8.44 (s, 1H), 11.62 (s, 1H)

[136]

[137] Preparation Example 8

[138] synthesis of 3-(trifluoromethoxy)benzaldehydeoxime

[139] In a similar manner as described in Preparation Example 1, by using 3-(trifluoromethoxy)benzaldehyde(38.03g, 200.0mmol), sodium hydroxide (12.00g, 300.0mmol) and hydrochloric acidhydroxylamine (16.6g, 240mmol), a white solid required compound (39.74g, 193mmol, 97%) was obtained.

[140] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.53 (m, 1H), 7.69 (m, 3H), 8.31 (s, 1H), 11.71 (s, 1H)

[141]

[142] Preparation Example 9

[143] synthesis of N-hydroxy-2-(trifluoromethyl)benzimidoylchloride

[144] 2-(trifluoromethyl)benzaldehydeoxime (30.0g, 158.60mmol) was dissolved in dimethylformimide (300mL), and added with N-chlorosuccinimide (23.31g, 174.46mmol), followed by stirring for 15 hours. After the reaction was completed, the resultant solution was vacuum evaporated, added with ethylacetate (1,500mL), washed with saturated sodium chloride aqueous solution (1,000mL) and purified water (1,000mL), respectively, dried with anhydrous sodium sulfate, and vacuum-evaporated to provide a pale yellow solid required compound(32.81g, 146.70mmol, 93%).

[145] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.73 (m, 2H), 7.80 (t, 1H), 7.86 (d, 1H), 12.61 (s, 1H)

[146]

[147] Preparation Example 10

[148] synthesis of 2-chloro-N-hydroxybenzimidoylchloride

[149] In a similar manner as described in Preparation Example 9, by using dimethyl-formamide (240mL), 2-chlorobenzaldehydeoxime (19.97g, 128.32mmol) and N-chlorosuccinimide(18.85g, 141.14mmol), a pale yellow solid required compound(20.04g, 105.21mmol, 82%) was obtained.

[150] ^{1}H-NMR(400㎒,$CDCl_3$, δ) = 7.46 (m, 1H), 7.54 (m. 1H), 7.58 (m, 2H), 12.54 (s, 1H)

[151]

[152] Preparation Example 11

[153] synthesis of 3-fluoro-N-hydroxybenzimidoylchloride

[154] In a similar manner as described in Preparation Example 9, by using dimethyl-formamide (240mL), 3-fluorobenzaldehydeoxime (20.0g, 143.77mmol) and N-chlorosuccinimide(21.12g, 158.12mmol), a pale yellow solid required compound(22.52g, 129.79mmol, 90%) was obtained.

[155] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.37 (m, 1H), 7.60 (m, 3H)

[156]

[157] Preparation Example 12

[158] synthesis of 2-fluoro-N-hydroxybenzimidoylchloride

[159] In a similar manner as described in Preparation Example 9, by using dimethyl-formamide (240mL), 2-fluorobenzaldehydeoxime (20.0g, 143.76mmol) and N-chlorosuccinimide (21.12g, 158.12mmol), a pale yellow solid required compound(23.32g, 134.40mmol, 94%) was obtained.

[160] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.29 (m, 1H), 7.47 (m, 1H), 7.62 (m, 2H)

[161]

[162] Preparation Example 13

[163] synthesis of N-hydroxy-4-(trifluoromethoxy)benzimidoylchloride

[164] In a similar manner as described in Preparation Example 9, by using dimethyl-formamide (240mL), 4-(trifluoromethoxy)benzaldehydeoxime (20.0g, 97.51mmol) and N-chlorosuccinimide (14.31g, 107.26mmol), a pale yellow solid required compound(21.10g, 88.04mmol, 90%) was obtained.

[165] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.47 (dd, 1H), 7.72 (tt, 2H), 12.60 (s, 1H)

[166]

[167] Preparation Example 14

[168] synthesis of N-hydroxy-2-(trifluoromethoxy)benzimidoylchloride

[169] In a similar manner as described in Preparation Example 9, by using dimethyl-formamide (240mL), 4-(trifluoromethoxy)benzaldehydeoxime (20.0g, 97.50mmol) and N-chlorosuccinimide (14.32g, 107.26mmol), a pale yellow solid required compound(19.48g, 81.30mmol, 83%)was obtained.

[170] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.49 (m, 1H), 7.62 (m, 1H), 7.68 (dd, 1H), 12.67 (s, 1H)

[171]

[172] Preparation Example 15

[173] synthesis of N-hydroxy-3-(trifluoromethyl)benzimidoylchloride

[174] In a similar manner as described in Preparation Example 9, by using 3-(trifluoromethyl)benzaldehydeoxime (30.0g, 158.60mmol), dimethylformimide (300mL) and N-chlorosuccinimide (23.31g, 174.46mmol), a pale yellow solid required compound(33.81g, 151.22mmol, 95%) was obtained.

[175] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.79 (m, 3H), 7.83 (m, 1H), 12.64 (s, 1H)

[176]

[177] Preparation Example 16

[178] synthesis of N-hydroxy-3-(trifluoromethoxy)benzimidoylchloride

[179] In a similar manner as described in Preparation Example 9, by using dimethyl-formamide (240mL), 3-(trifluoromethoxy)benzaldehydeoxime (20.0g, 97.50mmol) and N-chlorosuccinimide (14.32g, 107.26mmol), a pale yellow solid required compound(19.43g, 81.10mmol, 82%)was obtained.

[180] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 7.56 (m, 1H), 7.64 (m, 3H), 12.61 (s, 1H)

[181]

[182] Preparation Example 17

[183] synthesis of methyl-5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylate

[184] N-hydroxy-2-(trifluoromethyl)benzimidoylchloride (8.0g, 35.78mmol) and methylacetoacetate (8.30g, 71.56mmol) were dissolved in methanol (160mL). The resultant solution was stirred for 30 minutes while the reactor was cooled to -10℃ Then, sodium methoxide (5.80g, 107.34mmol) was slowly added thereto. The resultant product was warmed up to room temperature, stirred for 3 hours, and vacuum-evaporated to remove methanol. Then, ethylacetate (200mL) was added thereto. The resultant product was washed with purified water (200mL) and saturated sodium chloride aqueous solution (200mL), respectively, dried with anhydroussodium sulfate, and vacuum-evaporated. Through column chromatography, a purified white solid required compound(5.79g, 20.31mmol, 57%)was obtained.

[185] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.75 (s, 3H), 3.58 (s, 3H), 7.56 (m, 1H), 7.78 (m, 1H), 7.90 (m, 1H)

[186]

[187] Preparation Example 18

[188] synthesis of methyl-3-(2-chlorophenyl)-5-methylisoxazol-4-carboxylate

[189] In a similar manner as described in Preparation Example 17, by using methanol (160mL), 2-chloro-N-hydroxybenzimidoylchloride (8.0g, 42.10mmol), methylacetoacetate (9.78g, 84.20mmol) and sodium methoxide(6.83g, 126.30mmol), a white solid required compound (6.32g, 25.11mmol, 60%) was obtained.

[190] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.59 (s, 3H), 3.86 (s, 3H), 7.62 (m, 3H)

[191]

[192] Preparation Example 19

[193] synthesis of methyl-3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylate

[194] In a similar manner as described in Preparation Example 17, by using methanol (160mL), 3-fluoro-N-hydroxybenzimidoyl chloride (8.00g, 46.09mmol), methylacetoacetate (10.07g, 92.18mmol) and sodium methoxide(7.47g, 138.27mmol), a white solid required compound (7.60g, 32.14mmol, 70%) was obtained.

[195] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.58 (s, 3H), 3.91 (s, 3H), 7.21 (m, 1H), 7.42 (m, 3H)

[196]

[197] Preparation Example 20

[198] synthesis of methyl-3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylate

[199] In a similar manner as described in Preparation Example 17, by using methanol (160mL), 2-fluoro-N-hydroxybenzimidoyl chloride (8.00g, 46.09mmol), methylacetoacetate (10.07g, 92.18mmol) and sodium methoxide (7.47g, 138.27mmol), a white solid required compound (7.84g, 33.33mmol, 72%) was obtained.

[200] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.59 (s, 3H), 3.92 (s, 3H), 7.22 (m, 1H), 7.43 (m, 1H), 7.55 (m, 2H)

[201]

[202] Preparation Example 21

[203] synthesis of methyl-5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate

[204] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-4-(trifluoromethoxy)benzimidoylchloride (8.00g, 33.39mmol), methylacetoacetate (7.76g, 66.78mmol) and sodium methoxide (5.41g, 100.17mmol), a white solid required compound (6.74g, 22.36mmol, 67%) was obtained.

[205] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.71 (s, 3H), 3.73 (s, 3H), 7.48 (d, 2H), 7.76 (d, 2H)

[206]

[207] Preparation Example 22

[208] synthesis of methyl-5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate

[209] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-4-(trifluoromethoxy)benzimidoylchloride (8.00g, 33.39mmol), methylacetoacetate (7.76g, 66.78mmol) and sodium methoxide (5.41g, 100.17mmol), a white solid required compound (7.04g, 23.37mmol, 70%) was obtained.

[210] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.73 (s, 3H), 3.64 (s, 3H), 7.53 (m, 1H), 7.61 (m, 1H), 7.69 (m, 1H)

[211]

[212] Preparation Example 23

[213] synthesis of methyl-5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylate

[214] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-3-(trifluoromethyl)benzimidoylchloride (8.0g, 35.78mmol), methylacetoacetate (8.30g, 71.56mmol) and sodium methoxide (5.80g, 107.34mmol), a white solid required compound (5.82g, 20.41mmol, 57%) was obtained.

[215] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.73 (s, 3H), 3.56 (s, 3H), 7.58 (m, 1H), 7.97 (m, 3H)

[216]

[217] Preparation Example 24

[218] synthesis of methyl-5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate

[219] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-3-(trifluoromethoxy)benzimidoylchloride (8.00g, 33.39mmol), methylacetoacetate (7.76g, 66.78mmol) and sodium methoxide (5.41g, 100.17mmol), a white solid required compound (6.82g, 22.64mmol, 68%) was obtained.

[220] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.76 (s, 3H), 3.62 (s, 3H), 7.54 (m, 1H), 7.61 (m, 3H)

[221]

[222] Preparation Example 25

[223] synthesis of 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid

[224] methyl 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylate (6.0g, 21.03mmol) was dissolved in methanol (60mL), added with 3% sodium hydroxide aqueous solution (60mL), stirred at 30°Cfor 7hours, and vacuum-evaporated so as to remove methanol. The remaining solution was washed with ethyl acetate (20mL), and the aqueous layer was neutralized by a hydrochloric acid aqueous solution. Then, the produced crystal was filtered, washed with purified water (50mL), and dried so as to provide a white solid required compound (5.48g, 20.12mmol, 96%).

[225] ^{1}H-NMR(400㎒, DMSO, δ) = 2.69 (s, 3H), 7.49 (m, 1H), 7.72 (m, 1H), 7.83 (m, 1H), 13.12 (brs, 1H)

[226]

[227] Preparation Example 26

[228] synthesis of 3-(2-chlorophenyl)-5-methylisoxazol-4-carboxylic acid

[229] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-3-(2-chlorophenyl)-5-methylisoxazol-4-carboxylate (6.0g, 23.84mmol) and 3% sodium hydroxide aqueous solution(60mL), a white solid required compound(5.10g, 21.44mmol, 90%) was obtained.

[230] ^{1}H-NMR(400㎒, DMSO, δ) = 2.75 (s, 3H), 7.46 (m, 2H), 7.53(m, 1H), 7.59 (m, 1H), 13.00 (brs, 1H)

[231]

[232] Preparation Example 27

[233] synthesis of 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid

[234] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylate (6.0g, 25.51mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound(5.51g, 24.92mmol, 98%) was obtained.

[235] ^{1}H-NMR(400㎒, DMSO, δ) = 2.58 (s, 3H), 7.21 (m, 1H), 7.42 (m, 3H), 13.04 (brs, 1H)

[236]

[237] Preparation Example 28

[238] synthesis of 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid

[239] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylate (6.0g, 25.51mmol) and 3% sodium hydroxide aqueous solution(60mL), a white solid required compound (5.21g, 23.44mmol, 92%) was obtained.

[240] ^{1}H-NMR(400㎒, DMSO, δ) = 2.60 (s, 3H), 7.21 (m, 1H), 7.43 (m, 1H), 7.54 (m, 2H)

[241]

[242] Preparation Example 29

[243] synthesis of 5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid

[244] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate (6.0g, 19.91mmol) and 3% sodium hydroxide aqueous solution(60mL), a white solid required compound(5.55g, 19.32mmol, 97%) was obtained.

[245] ^{1}H-NMR(400㎒, DMSO, δ) = 2.71 (s, 3H), 7.48 (d, 2H), 7.76 (d, 2H), 13.15 (brs, 1H)

[246]

[247] Preparation Example 30

[248] synthesis of 5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid

[249] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate (6.0g, 19.91mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound (5.34g, 18.59mmol, 93%) was obtained.

[250] ^{1}H-NMR(400㎒, DMSO, δ) = 2.72 (s, 3H), 7.50 (m, 2H), 7.58 (m, 1H), 7.67 (m, 1H), 13.62 (brs, 1H)

[251]

[252] Preparation Example 31

[253] synthesis of 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid

[254] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylate (6.0g, 21.03mmol) and 3% sodium hydroxide aqueous solution(60mL), a white solid required compound(5.37g, 19.80mmol, 94%) was obtained.

[255] ^{1}H-NMR(400㎒, DMSO, δ) = 2.67 (s, 3H), 7.48 (m, 1H), 7.80 (m, 3H), 13.11 (brs, 1H)

[256]

[257] Preparation Example 32

[258] synthesis of 5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid

[259] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate(6.0g, 19.91mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound(5.47g, 19.04mmol, 96%) was obtained.

[260] ^{1}H-NMR(400㎒, DMSO, δ) = 2.71 (s, 3H), 7.48 (m, 2H), 7.64 (m, 2H), 13.57 (brs, 1H)

[261]

[262] Preparation Example 33

[263] synthesis of methyl-5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylate

[264] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-2-(trifluoromethyl)benzimidoyl chloride (8.00g, 33.39mmol),

methylcyanoacetate (4.14g, 41.74mmol) and sodium methoxide (3.61g, 66.78mmol), a white solid required compound (8.13g, 28.42mmol, 85%) was obtained.

[265] ^{1}H-NMR(400㎒, DMSO, δ) = 3.59 (s, 3H), 6.12 (brs, 2H), 7.36 (m, 1H), 7.57 (m, 2H), 7.69 (m, 1H)

[266]

[267] Preparation Example 34

[268] synthesis of methyl-5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylate

[269] In a similar manner as described in Preparation Example 17, by using methanol (160mL), 2-chloro-N-hydroxybenzimidoylchloride (8.00g, 42.10mmol), methyl-cyanoacetate (5.22g, 52.63mmol) and sodium methoxide (4.55g, 84.20mmol), a white solid required compound(9.40g, 37.21mmol, 88%) was obtained.

[270] ^{1}H-NMR(400㎒, DMSO, δ) = 3.65 (s, 3H), 6.20(brs, 2H), 7.41 (m, 4H)

[271]

[272] Preparation Example 35

[273] synthesis of methyl 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylate

[274] In a similar manner as described in Preparation Example 17, by using methanol (160mL), 3-fluoro-N-hydroxybenzimidoyl chloride (8.00g, 46.09mmol), methyl-cyanoacetate (5.94g, 59.92mmol) and sodium methoxide (4.98g, 92.18mmol), a white solid required compound (8.42g, 35.64mmol, 77%) was obtained.

[275] ^{1}H-NMR(400㎒, CDCl3, δ) = 3.92 (s, 3H), 6.30 (brs, 2H), 7.21 (m, 1H), 7.42 (m, 3H)

[276]

[277] Preparation Example 36

[278] synthesis of methyl-5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylate

[279] In a similar manner as described in Preparation Example 17, by using methanol (160mL), 2-fluoro-N-hydroxybenzimidoyl chloride (8.00g, 46.09mmol), methyl-cyanoacetate (5.94g, 59.92mmol) and sodium methoxide (4.98g, 92.18mmol), a white solid required compound(8.23g, 34.82mmol, 76%) was obtained.

[280] ^{1}H-NMR(400㎒, CDCl3, δ) = 3.89 (s, 3H), 6.31 (brs, 2H), 7.22 (m, 1H), 7.41 (m, 1H), 7.55 (m, 2H)

[281]

[282] Preparation Example 37

[283] synthesis of methyl 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate

[284] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-4-(trifluoromethoxy)benzimidoylchloride (8.00g, 33.39mmol), methylcyanoacetate (4.31g, 43.41mmol) and sodium methoxide (3.61g, 66.78mmol), a white solid required compound(8.27g, 27.35mmol, 82%) was obtained.

[285] ^{1}H-NMR(400㎒, DMSO, δ) = 3.51 (s, 3H), 6.21 (brs, 2H), 7.26 (d, 2H), 7.77 (d, 2H)

[286]

[287] Preparation Example 38

[288] synthesis of methyl 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate

[289] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-2-(trifluoromethoxy)benzimidoylchloride (8.00g, 33.39mmol), methylcyanoacetate (4.31g, 43.41mmol) and sodium methoxide (3.61g, 66.78mmol), a white solid required compound(9.07g, 30.02mmol, 90%) was obtained.

[290] ^{1}H-NMR(400㎒,DMSO, δ) = 3.38 (s, 3H), 6.18 (brs, 2H), 7.41 (m, 2H), 7.42 (m, 1H), 7.47 (m, 1H)

[291]

[292] Preparation Example 39

[293] synthesis of methyl-5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylate

[294] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-3-(trifluoromethyl)benzimidoylchloride (8.00g, 33.39mmol), methylcyanoacetate (4.14g, 41.74mmol) and sodium methoxide (3.61g, 66.78mmol), a white solid required compound(7.46g, 26.06mmol, 78%) was obtained.

[295] ^{1}H-NMR(400㎒, DMSO, δ) = 3.61 (s, 3H), 6.11 (brs, 2H), 7.32 (m, 1H), 7.62 (m, 3H)

[296]

[297] Preparation Example 40

[298] synthesis of methyl-5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate

[299] In a similar manner as described in Preparation Example 17, by using methanol (160mL), N-hydroxy-3-(trifluoromethoxy)benzimidoylchloride (8.00g, 33.39mmol), methylcyanoacetate (4.31g, 43.41mmol) and sodium methoxide (3.61g, 66.78mmol), a white solid required compound(8.42g, 27.87mmol, 83%) was obtained.

[300] ^{1}H-NMR(400㎒,DMSO, δ) = 3.42 (s, 3H), 6.22 (brs, 2H), 7.46 (m, 2H), 7.53 (m, 2H)

[301]

[302] Preparation Example 41

[303] synthesis of 5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid

[304] In a similar manner as described in Preparation Example 25, by using methanol (60mL), 5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylate (6.0g, 20.96mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound(4.06g, 14.92mmol, 71%) was obtained.

[305] ^{1}H-NMR(400㎒, DMSO, δ) = 7.40 (m, 1H), 7.70 (m, 2H), 7.76 (m, 1H), 7.81 (brs, 2H), 12.18 (brs, 1H)

[306]

[307] Preparation Example 42

[308] synthesis of 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid

[309] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylate (6.0g, 23.75mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound(3.66g, 15.33mmol, 65%) was obtained.

[310] ^{1}H-NMR(400㎒, DMSO, δ) = 7.45 (m, 3H), 7.54 (m, 1H), 7.85 (brs, 2H), 12.04 (brs, 1H)

[311]

[312] Preparation Example 43

[313] synthesis of 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid

[314] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylate (6.0g, 25.40mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound(3.08g, 13.86mmol, 55%) was obtained.

[315] ^{1}H-NMR(400㎒, DMSO, δ) = 6.28 (brs, 2H), 7.20 (m, 1H), 7.44 (m, 3H)

[316]

[317] Preparation Example 44

[318] synthesis of 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid

[319] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylate (6.0g, 25.40mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound(3.18g, 14.33mmol, 56%) was obtained.

[320] ^{1}H-NMR(400㎒, DMSO, δ) = 6.22 (brs, 2H), 7.25 (m, 1H), 7.45 (m, 1H), 7.59 (m, 2H), 12.13 (brs, 1H)

[321]

[322] Preparation Example 45

[323] synthesis of 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid

[324] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate (6.0g, 19.85mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound (4.32g, 15.02mmol, 76%) was obtained.

[325] ^{1}H-NMR(400㎒, DMSO, δ) = 7.31 (d, 2H), 7.83 (d, 2H), 7.85 (brs, 2H), 12.01 (brs, 1H)

[326]

[327] Preparation Example 46

[328] synthesis of 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid

[329] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl-5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate (6.0g, 19.85mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid

required compound(4.00g, 13.89mmol, 70%) was obtained.

[330] ^{1}H-NMR(400㎒, DMSO, δ) = 7.45 (m, 3H), 7.59 (m, 1H), 7.82 (brs, 2H), 12.04 (brs, 1H)

[331]

[332] Preparation Example 47

[333] synthesis of 5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid

[334] In a similar manner as described in Preparation Example 25, by using methanol (60mL), 5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylate (6.0g, 20.96mmol) and 3% sodium hydroxide aqueous solution(60mL), a white solid required compound(4.14g, 15.21mmol, 73%) was obtained.

[335] ^{1}H-NMR(400㎒, DMSO, δ) = 7.34 (m, 1H), 7.68 (m, 3H), 7.87 (brs, 2H), 12.31 (brs, 1H)

[336]

[337] Preparation Example 48

[338] synthesis of 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid

[339] In a similar manner as described in Preparation Example 25, by using methanol (60mL), methyl 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylate (6.0g, 19.85mmol) and 3% sodium hydroxide aqueous solution (60mL), a white solid required compound(4.16g, 14.43mmol, 73%) was obtained.

[340] ^{1}H-NMR(400㎒, DMSO, δ) = 7.43 (m, 3H), 7.63 (m, 1H), 7.84 (brs, 2H), 12.04 (brs, 1H)

[341]

[342] Example 1

[343] synthesis of (4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[344] 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine(332mg, 1.84mmol) were dissolved in dichloromethane (30mL), and stirred at room temperature for 8 hours. The resultant solution was washed with saturated sodium carbonate aqueous solution (30mL), purified water (30mL) and saturated sodium chloride aqueous solution (30mL), respectively. Then, the organic layer was dried with anhydrous sodium sulfate, concentrated, and purified with column chromatographyso as to provide a white solid required compound (528mg, 1.34mmol, 73%).

[345] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.56 (s, 3H), 2.73 (brs, 2H), 3.01 (brs, 2H), 3.41 (brs, 2H), 3.72 (brs, 2H), 6.04 (m, 3H), 6.81 (t, 1H), 7.49 (m, 1H), 7.72 (m, 1H), 7.83 (m, 1H)

[346]

[347] Example 2

[348] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[349] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine (425mg, 1.84mmol), a white solid required compound(644mg, 1.33mmol, 72%) was obtained.

[350] ^{1}H-NMR(400㎒, CDCl3, δ) = 2.58 (s, 3H), 2.75 (brs, 2H), 3.03 (brs, 2H), 3.42 (brs, 2H), 3.74 (brs, 2H), 6.69 (dd, 1H), 6.89 (d, 1H), 7.28 (m, 1H), 7.55 (d, 1H), 7.64 (m, 2H), 7.82 (d, 2H)

[351]

[352] Example 3

[353] synthesis of (4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[354] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (354mg, 1.84mmol), a gel-like required compound (602mg, 1.35mmol, 73%) was obtained.

[355] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.64 (brs, 2H), 2.67 (s, 3H), 3.13 (brs, 2H), 3.38 (brs, 2H), 4.06 (brs, 2H), 6.43 (brs, 1H), 6.53 (m, 2H), 7.39 (dd, 1H), 7.49 (m, 1H), 7.70 (m, 1H), 7.80 (dd, 1H), 7.81 (m, 1H)

[356]

[357] Example 4

[358] synthesis of (4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[359] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(504mg, 1.13mmol, 62%) was obtained.

[360] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.59 (S, 3H), 2.75 (brs, 2H), 3.06 (brs, 2H), 3.42 (brs, 2H), 3.76 (brs, 2H), 3.82 (s, 3H), 6.49 (brs, 1H), 6.49 (m, 2H), 7.19 (t, 1H), 7.55 (d,

1H), 7.67 (m, 2H), 7.82 (d, 1H)

[361]

[362] Example 5

[363] synthesis of (5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[364] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine(424mg, 1.84mmol), a gel-like required compound (593mg, 1.23mmol, 67%) was obtained.

[365] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.63 (brs, 2H), 2.69 (s, 3H), 3.15 (brs, 2H), 3.37 (brs, 2H), 3.39 (brs, 2H), 4.02 (brs, 2H), 6.91 (m, 2H), 7.03 (m, 1H), 7.26 (m, 1H), 7.51 (m, 1H), 7.70 (m, 2H), 7.82 (m, 1H)

[366]

[367] Example 6

[368] synthesis of (4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[369] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol (328mg, 1.84mmol), a white solid required compound (467mg, 1.08mmol, 59%) was obtained.

[370] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.64 (brs, H), 2.69 (s, 3H), 3.91 (brs, 4H), 6.78 (m, 4H), 7.49 (m, 2H), 7.72 (m, 1H), 7.83 (m, 1H)

[371]

[372] Example 7

[373] synthesis of (4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[374] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol (328mg, 1.84mmol), a white solid required compound(451mg, 1.05mmol, 57%) was obtained.

[375] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.49 (brs, 2H), 2.61 (s, 3H), 2.78 (brs, 2H), 3.50 (brs, 2H), 3.80 (brs, 2H), 6.93 (m, 3H), 7.13 (m, 1H), 7.58 (m, 1H), 7.70 (m, 2H), 7.86 (m,

1H)

[376]

[377] Example 8

[378] synthesis of (4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[379] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound (548mg, 1.26mmol, 69%)was obtained.

[380] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.68 (s, 3H), 2.91 (brs, 4H), 3.42 (brs, 4H), 6.91 (m, 2H), 7.05 (m, 2H), 7.45 (m, 1H), 7.71 (m, 1H), 7.82 (m, 1H)

[381]

[382] Example 9

[383] synthesis of (3-(2-chlorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[384] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(2-chlorophenyl)-5-methylisoxazol-4-carboxylic acid (437mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(576mg, 1.40mmol, 76%) was obtained.

[385] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.61 (s, 3H), 3.10 (brs, 2H), 3.33 (brs, 2H), 3.74 (brs, 4H), 3.79 (s, 3H), 6.36 (t, 1H), 6.46 (m, 2H), 7.18 (t, 1H), 7.41 (m, 2H), 7.50 (m, 1H), 7.56 (dd, 1H)

[386]

[387] Example 10

[388] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[389] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(562mg, 1.41mmol, 76%) was obtained.

[390] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.70 (brs, 2H), 3.14 (brs, 2H), 3.28 (brs, 2H), 3.96 (brs, 2H), 6.70 (m, 2H), 7.02 (m, 2H), 7.17 (m, 1H), 7.45 (m, 3H)

[391]

[392] Example 11

[393] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)methanone

[394] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(619mg, 1.43mmol, 78%) was obtained.

[395] ^{1}H-NMR ($CDCl_3$, 400MHz, δ) = 2.56 (s, 3H), 2.66 (brs, 2H), 3.16 (brs, 2H), 3.27 (brs, 2H), 3.91 (brs, 2H), 6.67 (dd, 1H), 6.88 (d, 1H), 7.19 (m, 1H), 7.29 (m, 1H), 7.44 (m, 3H)

[396]

[397] Example 12

[398] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[399] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(612mg, 1.55mmol, 84%) was obtained.

[400] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.73 (brs, 2H), 3.19 (brs, 2H), 3.30 (brs, 2H), 3.80 (s, 3H), 3.93 (brs, 2H), 6.41(m, 1H), 6.49 (m, 2H), 7.18 (m, 2H), 7.46 (m, 3H)

[401]

[402] Example 13

[403] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[404] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(586mg, 1.48mmol, 81%) was obtained.

[405] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.61 (brs, 2H), 3.07 (brs, 2H), 3.34 (brs, 2H), 3.86 (s, 3H), 3.97 (brs, 2H), 6.53 (m, 1H), 6.90 (m, 2H), 7.18 (m, 1H), 7.05

(m, 1H), 7.46 (m, 3H)

[406]

[407] Example 14

[408] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[409] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a white solid required compound(506mg, 1.17mmol, 64%) was obtained.

[410] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.59 (brs, 2H), 3.03 (brs, 2H), 3.32 (brs, 2H), 3.88 (brs, 2H), 6.99 (m, 1H), 7.21 (m, 4H), 7.42 (m, 3H)

[411]

[412] Example 15

[413] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[414] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol (424mg, 1.84mmol), a white solid required compound(486mg, 1.27mmol, 69%) was obtained.

[415] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.61 (brs, 2H), 3.07 (brs, 2H), 3.32 (brs, 2H), 3.95 (brs, 2H), 6.78 (m, 4H), 7.19 (m, 1H), 7.45 (m, 3H)

[416]

[417] Example 16

[418] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[419] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol (424mg, 1.84mmol), a white solid required compound (462mg, 1.21mmol, 66%) was obtained.

[420] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.58 (s, 3H), 2.63 (brs, 2H), 3.00 (brs, 2H), 3.39 (brs, 2H), 4.02 (brs, 2H), 6.89 (m, 1H), 7.01 (m, 2H), 7.17 (m, 1H), 7.24 (m, 1H), 7.45 (m, 1H), 7.51 (m, 2H)

[421]

[422] Example 17

[423] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[424] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(511mg, 1.33mmol, 72%) was obtained.

[425] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.55 (s, 3H), 2.66 (brs, 2H), 2.99 (brs, 2H), 3.44 (brs, 2H), 3.88 (brs, 2H), 6.74 (m, 2H), 7.03 (m, 2H), 7.17 (m, 1H), 7.45 (m, 3H)

[426]

[427] Example 18

[428] synthesis of (3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[429] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(578mg, 1.51mmol, 82%) was obtained.

[430] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.71 (brs, 2H), 3.06 (brs, 2H), 3.38 (brs, 2H), 3.75 (brs, 2H), 6.10 (m, 3H), 6.79 (t, 1H), 7.19 (m, 1H), 7.40 (m, 1H), 7.57 (m, 2H)

[431]

[432] Example 19

[433] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)methanone

[434] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine (425mg, 1.84mmol), a white solid required compound(587mg, 1.35mmol, 74%) was obtained.

[435] ^{1}H-NMR ($CDCl_3$, 400MHz, δ) = 2.57 (s, 3H), 2.79 (brs, 2H), 3.01 (brs, 2H), 3.40 (brs, 2H), 3.73 (brs, 2H), 6.65 (dd, 1H), 6.87 (d, 1H), 7.16 (m, 1H), 7.27 (m, 1H), 7.40 (m, 1H), 7.54 (m, 2H)

[436]

[437] Example 20

[438] synthesis of (3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[439] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(622mg, 1.57mmol, 86%) was obtained.

[440] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.57 (s, 3H), 2.63 (brs, 2H), 3.11 (brs, 2H), 3.32 (brs, 2H), 3.83 (brs, 2H), 3.82 (s, 3H), 6.43 (brs, 1H), 6.48 (m, 2H), 7.19 (m, 1H), 7.42 (m, 1H), 7.46 (dd, 1H), 7.54 (m, 1H), 7.78 (dd, 2H)

[441]

[442] Example 21

[443] synthesis of (3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[444] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(532mg, 1.35mmol, 73%) was obtained.

[445] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.61 (brs, 2H), 2.99 (brs, 2H), 3.31 (brs, 2H), 3.79 (brs, 2H), 3.83 (s, 3H), 6.78 (brs, 1H), 6.84 (t, 1H), 6.91 (t, 1H), 7.19 (m, 1H), 7.42 (m, 1H), 7.59 (m, 2H), 7.69 (dd, 1H)

[446]

[447] Example 22

[448] synthesis of (3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[449] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a white solid required compound (501mg, 1.15mmol, 63%) was obtained.

[450] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.55 (s, 3H), 2.62 (brs, 2H), 3.03 (brs, 2H), 3.38 (brs, 2H), 7.02 (m, 2H), 7.19 (m, 1H), 7.23 (m, 1H), 7.42 (m, 1H), 7.54 (m, 2H)

[451]

[452] Example 23

[453] synthesis of (3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[454] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol (424mg, 1.84mmol), a white solid required compound (542mg, 1.42mmol, 77%) was obtained.

[455] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.56 (s, 3H), 2.61 (brs, 2H), 3.07 (brs, 2H), 3.32 (brs, 2H), 3.95 (brs, 2H), 6.78 (m, 4H), 7.19 (m, 1H), 7.40 (m, 1H), 7.57 (m, 2H)

[456]

[457] Example 24

[458] synthesis of (3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[459] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol (424mg, 1.84mmol), a white solid required compound (433mg, 1.13mmol, 62%) was obtained.

[460] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.57 (s, 3H), 2.61 (brs, 2H), 3.04 (brs, 2H), 3.35 (brs, 2H), 4.01 (brs, 2H), 6.91 (m, 1H), 7.03 (m, 2H), 7.17 (m, 1H), 7.20 (m, 1H), 7.43 (m, 1H), 7.58 (m, 2H)

[461]

[462] Example 25

[463] synthesis of (3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[464] In a similar manner as described in Example 1, by using dichloromethane (30mL), 3-(2-fluorophenyl)-5-methylisoxazol-4-carboxylic acid (407mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(538mg, 1.40mmol, 76%) was obtained.

[465] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.55 (s, 3H), 2.87 (brs, 4H), 3.05 (brs, 4H), 6.91 (m, 2H), 7.04 (m, 2H), 7.19 (m, 1H), 7.43 (m, 1H), 7.59 (m, 2H)

[466]

[467] Example 26

[468] synthesis of (4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[469] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(536mg, 1.20mmol, 65%) was obtained.

[470] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.56 (s, 3H), 2.63 (brs, 2H), 3.06 (brs, 2H), 3.33 (brs, 2H), 3.94 (brs, 2H), 6.80 (t, 1H), 6.04 (m, 3H), 7.32 (d, 2H), 7.76 (d, 2H)

[471]

[472] Example 27

[473] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[474] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine (425mg, 1.84mmol), a gel-like required compound(589mg, 1.17mmol, 64%) was obtained.

[475] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.55 (s, 3H), 2.68 (brs, 2H), 3.15 (brs, 2H), 3.28 (brs, 2H), 3.89 (brs, 2H), 6.65 (dd, 1H), 6.87 (d, 1H), 7.28 (t, 1H), 7.32 (dd, 2H), 7.74 (dd, 2H)

[476]

[477] Example 28

[478] synthesis of (4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[479] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (353mg, 1.84mmol), a white solid required compound (622mg, 1.35mmol, 73%) was obtained.

[480] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.59 (s, 3H), 2.64 (brs, 2H), 3.17 (brs, 2H), 3.29 (brs, 2H), 3.75 (brs, 2H), 3.80 (s, 3H), 6.42 (brs, 1H), 6.52 (m, 2H), 7.43 (dd, 1H), 7.47 (d, 2H), 7.75 (d, 2H), 7.78 (dd, 1H)

[481]

[482] Example 29

[483] synthesis of (4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[484] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine (353mg, 1.84mmol), a white solid required compound(604mg, 1.33mmol, 72%) was obtained.

[485] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.60 (brs, 5H), 2.98 (brs, 2H), 3.31 (brs, 2H), 3.85 (s, 3H), 6.76 (s, 1H), 6.87 (t, 1H), 6.91 (t, 1H), 7.65 (dd, 1H), 7.43 (d, 2H), 7.73 (d, 2H), 7.78 (brs, 2H)

[486]

[487] Example 30

[488] synthesis of (5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[489] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a gel-like required compound(574mg, 1.15mmol, 63%) was obtained.

[490] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.61 (s, 3H), 2.65 (brs, 2H), 3.13 (brs, 2H), 3.32 (brs, 2H), 7.10 (m, 2H), 7.14 (d, 1H), 7.41 (m, 1H), 7.46 (d, 2H), 7.77 (d, 2H)

[491]

[492] Example 31

[493] synthesis of (4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[494] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(502mg, 1.12mmol, 61%) was obtained.

[495] ^{1}H-NMR(400㎒, DMSO, δ) = 2.60 (brs, 2H), 2.62 (s, 3H), 3.08 (brs, 2H), 3.29 (brs, 2H), 3.91 (brs, 2H), 6.74 (m, 2H), 6.74 (m, 2H), 7.46 (d, 2H), 7.78 (d, 2H)

[496]

[497] Example 32

[498] synthesis of (4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[499] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(538mg, 1.02mmol, 65%) was obtained.

[500] ^{1}H-NMR (400㎒, DMSO, δ) = 2.62 (s, 3H), 2.63 (brs, 2H), 3.01 (brs, 2H), 3.38 (brs, 2H), 4.02 (brs, 2H), 6.87 (m, 1H), 7.08 (m, 2H), 7.25 (m, 1H), 7.43 (d, 2H), 7.73 (d, 2H)

[501]

[502] Example 33

[503] synthesis of (4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(4-trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[504] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(4-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(610mg, 1.35mmol, 74%) was obtained.

[505] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.62 (s, 3H), 2.91 (brs, 4H), 4.47 (brs, 4H), 6.96 (m, 2H), 7.07 (m, 2H), 7.44 (d, 2H), 7.75 (d, 2H)

[506]

[507] Example 34

[508] synthesis of (4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[509] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(593mg, 1.32mmol, 72%) was obtained.

[510] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.56 (brs, 2H), 2.61 (s, 3H), 3.01 (brs, 2H), 3.31 (brs, 2H), 3.81 (brs, 2H), 6.80 (t, 1H), 6.99 (m, 2H), 7.05 (m, 1H), 7.40 (m, 1H), 7.44 (dd, 1H), 7.55 (m, 1H), 7.77 (dd, 1H)

[511]

[512] Example 35

[513] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[514] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine (381mg, 1.84mmol), a white solid required compound(652mg, 1.30mmol, 71%) was obtained.

[515] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.60 (s, 3H), 2.61 (brs, 2H), 3.09 (brs, 2H), 3.27 (brs, 2H), 3.70 (brs, 2H), 6.66 (dd, 1H), 6.86 (d, 1H), 7.29 (t, 1H), 7.39 (d, 1H), 7.43 (t, 1H), 7.55 (t, 1H), 7.66 (dd, 1H)

[516]

[517] Example 36

[518] synthesis of (4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[519] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (354mg, 1.84mmol), a gel-like required compound(564mg, 1.22mmol, 66%) was obtained.

[520] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.60 (s, 3H), 2.65 (brs, 2H), 3.12 (brs, 2H), 3.31 (brs, 2H), 3.79 (brs, 2H), 3.81 (s, 3H), 6.40 (brs, 1H), 6.50 (m, 2H), 7.19 (t, 1H), 7.39 (m, 1H), 7.44 (dd, 1H), 7.54 (m, 1H), 7.77 (dd, 1H)

[521]

[522] Example 37

[523] synthesis of (4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[524] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(570mg, 1.24mmol, 67%) was obtained.

[525] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.60 (brs, 2H), 2.61 (S, 3H), 2.99 (brs, 2H), 3.33 (brs, 2H), 3.78 (brs, 2H), 3.85 (s, 3H), 6.77 (brs, 1H), 6.89 (t, 1H), 6.92 (t, 1H), 7.05 (t, 1H), 7.42 (m, 2H), 7.55 (t, 1H), 7.66 (dd, 1H)

[526]

[527] Example 38

[528] synthesis of (5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl) piperazine-1-yl)methanone

[529] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a gel-like required compound(486mg, 0.97mmol, 53%) was obtained.

[530] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.61 (s, 3H), 2.69 (brs, 2H), 3.17 (brs, 2H), 3.32 (brs, 2H), 3.82 (brs, 2H), 7.01 (d, 1H), 7.02 (s, 1H), 7.16 (d, 1H), 7.40 (m, 2H), 7.45 (t, 1H), 7.55 (t, 1H), 7.68 (dd, 1H)

[531]

[532] Example 39

[533] synthesis of (4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxaz ol-4-yl)methanone

[534] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(502mg, 1.12mmol, 61%) was obtained.

[535] ^{1}H-NMR(400㎒, DMSO, δ) = 2.61 (brs, 2H), 2.64 (s, 3H), 3.04 (brs, 2H), 3.29(brs, 2H), 3.91 (brs, 2H), 6.76 (m, 4H), 7.53 (m, 2H), 7.60 (m, 1H), 7.69 (m, 1H)

[536]

[537] Example 40

[538] synthesis of (4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxaz ol-4-yl)methanone

[539] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol (328mg, 1.84mmol), a white solid required compound(536mg, 1.20mmol, 65%) was obtained.

[540] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.39 (brs, 2H), 2.63 (s, 3H), 2.89 (brs, 2H), 3.36 (brs, 2H), 3.86 (brs, 2H), 6.89 (m, 1H), 6.98 (m, 2H), 7.15 (m, 1H), 7.47 (m, 2H), 7.76 (m, 1H), 7.68 (dd, 1H)

[541]

[542] Example 41

[543] synthesis of (4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[544] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(2-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(536mg, 1.20mmol, 65%) was obtained.

[545] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.63 (s, 3H), 2.91 (brs, 4H), 3.51 (brs, 4H), 6.94 (m, 2H), 7.07 (m, 2H), 7.53 (m, 2H), 7.63 (m, 1H), 7.74 (m, 1H)

[546]

[547] Example 42

[548] synthesis of (4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[549] In a similar manner as described in Example 1, by using dichloromethane (30mL), methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(536mg, 1.24mmol, 67%) was obtained.

[550] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.68 (s, 3H), 2.73 (brs, 2H), 3.01 (brs, 2H), 3.41 (brs, 2H), 3.72 (brs, 2H), 6.09 (m, 3H), 6.83 (t, 1H), 7.34 (m, 1H), 7.72 (m, 1H), 7.86 (m, 2H)

[551]

[552] Example 43

[553] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[554] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine (425mg, 1.84mmol), a white solid required compound(644mg, 1.24mmol, 68%) was obtained.

[555] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.62 (s, 3H), 2.73 (brs, 2H), 3.12 (brs, 2H), 3.48 (brs, 2H), 3.76 (brs, 2H), 6.70 (dd, 1H), 6.84 (d, 1H), 7.31 (m, 1H), 7.54 (d, 1H), 7.72 (m, 1H), 7.82 (m, 2H)

[556]

[557] Example 44

[558] synthesis of (4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[559] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (354mg, 1.84mmol), a gel-like required compound(602mg, 1.37mmol, 75%) was obtained.

[560] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.61 (brs, 2H), 2.69 (s, 3H), 3.15 (brs, 2H), 3.46 (brs, 2H), 4.12 (brs, 2H), 6.48 (brs, 1H), 6.6.50 (m, 2H), 7.31 (dd, 1H), 7.37 (m, 1H), 7.75 (m, 1H), 7.85 (m, 2H)

[561]

[562] Example 45

[563] synthesis of (4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[564] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(524mg, 1.18mmol, 64%) was obtained.

[565] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.59 (S, 3H), 2.73 (brs, 2H), 2.08 (brs, 2H), 3.41 (brs, 2H), 3.73 (brs, 2H), 3.84 (s, 3H), 6.47 (brs, 1H), 6.52 (m, 2H), 7.13 (t, 1H), 7.32 (m, 1H), 7.76 (m, 1H), 7.83 (m, 2H)

[566]

[567] Example 46

[568] synthesis of (5-methyl-3-(3-trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[569] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a gel-like required compound(501mg, 1.04mmol, 56%) was obtained.

[570] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.60 (brs, 2H), 2.62 (s, 3H), 3.28 (brs, 2H), 3.42 (brs, 2H), 3.54 (brs, 2H), 4.03 (brs, 2H), 6.92 (m, 2H), 7.04 (m, 1H), 7.32 (m, 1H), 7.76 (m, 2H), 7.85 (m, 2H)

[571]

[572] Example 47

[573] synthesis of (4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[574] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol (328mg, 1.84mmol), a white solid required compound(438mg, 1.02mmol, 55%) was obtained.

[575] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.67 (s, 3H), 2.71 (brs, 4H), 3.89 (brs, 4H), 6.81 (m, 4H), 7.36 (m, 1H), 7.72 (m, 1H), 7.86 (m, 2H)

[576]

[577] Example 48

[578] synthesis of (4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[579] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol (328mg, 1.84mmol), a white solid required compound(466mg, 1.08mmol, 59%) was obtained.

[580] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.48 (brs, 2H), 2.64 (s, 3H), 2.77 (brs, 2H), 3.53 (brs, 2H), 3.87 (brs, 2H), 6.92 (m, 3H), 7.19 (m, 1H), 7.36 (m, 1H), 7.72 (m, 1H), 7.84 (m, 2H)

[581]

[582] Example 49

[583] synthesis of (4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone

[584] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound (566mg, 1.31mmol, 71%) was obtained.

[585] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.68 (s, 3H), 2.94 (brs, 4H), 3.38 (brs, 4H), 6.94 (m, 2H), 7.06 (m, 2H), 7.39 (m, 1H), 7.75 (m, 1H), 7.84 (m, 2H)

[586]

[587] Example 50

[588] synthesis of (4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[589] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(542mg, 1.21mmol, 65%) was obtained.

[590] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.53 (brs, 2H), 2.41 (s, 3H), 3.03 (brs, 2H), 3.48 (brs, 2H), 3.79 (brs, 2H), 6.84 (t, 1H), 7.02 (m, 2H), 7.06 (m, 2H), 7.42 (m, 2H), 7.61 (m, 2H)

[591]

[592] Example 51

[593] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[594] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine (381mg, 1.84mmol), a white solid required compound(602mg, 1.20mmol, 65%) was obtained.

[595] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.59 (brs, 2H), 2.72 (s, 3H), 3.12 (brs, 2H), 3.28 (brs, 2H), 3.70 (brs, 2H), 6.69 (dd, 1H), 6.82 (d, 1H), 7.20 (t, 1H), 7.44 (m, 2H), 7.58 (m, 2H)

[596]

[597] Example 52

[598] synthesis of (4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[599] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (354mg, 1.84mmol), a gel-like required compound(564mg, 1.22mmol, 66%) was obtained.

[600] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.69 (s, 3H), 2.72 (brs, 2H), 3.16 (brs, 2H), 3.33 (brs, 2H), 3.82 (brs, 2H), 3.83 (s, 3H), 6.42 (brs, 1H), 6.58 (m, 2H), 7.22 (t, 1H), 7.44 (m, 2H), 7.59 (m, 2H)

[601]

[602] Example 53

[603] synthesis of (4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[604] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(633mg, 1.37mmol, 75%) was obtained.

[605] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.68 (brs, 2H), 2.70 (S, 3H), 2.98 (brs, 2H), 3.43 (brs, 2H), 3.87 (brs, 2H), 3.82 (s, 3H), 6.76 (brs, 1H), 6.91 (t, 1H), 6.96 (t, 1H), 7.04 (t, 1H), 7.41 (m, 2H), 7.65 (m, 2H)

[606]

[607] Example 54

[608] synthesis of (5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-trifluoromethyl)phenyl)piperazine-1-yl)methanone

[609] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a gel-like required compound(501mg, 1.00mmol, 55%) was obtained.

[610] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.64 (s, 3H), 2.70 (brs, 2H), 3.21 (brs, 2H), 3.30 (brs, 2H), 3.84 (brs, 2H), 7.02 (d, 1H), 7.08 (s, 1H), 7.18 (d, 1H), 7.40 (m, 1H), 7.43 (m, 2H), 7.68 (m, 2H)

[611]

[612] Example 55

[613] synthesis of (4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[614] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(502mg, 1.12mmol, 61%) was obtained.

[615] ^{1}H-NMR(400㎒, DMSO, δ) = 2.62 (brs, 4H), 2.69 (s, 3H), 3.49 (brs, 4H), 6.74 (m, 4H), 7.47 (m, 2H), 7.69 (m, 2H)

[616]

[617] Example 56

[618] synthesis of (4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[619] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol (328mg, 1.84mmol), a white solid required compound(536mg, 1.20mmol, 65%) was obtained.

[620] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.34 (brs, 2H), 2.63 (s, 3H), 2.85 (brs, 2H), 3.35 (brs, 2H), 3.84 (brs, 2H), 6.85 (m, 1H), 6.97 (m, 2H), 7.20 (m, 1H), 7.45 (m, 2H), 7.69 (m, 2H)

[621]

[622] Example 57

[623] synthesis of (4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone

[624] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-methyl-3-(3-(trifluoromethoxy)isoxazol-4-carboxylic acid (500mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(536mg, 1.20mmol, 65%) was obtained.

[625] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.64 (s, 3H), 2.94 (brs, 4H), 3.58 (brs, 4H), 6.90 (m, 2H), 7.21 (m, 2H), 7.50 (m, 2H), 7.63 (m, H)

[626]

[627] Example 58

[628] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[629] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440 mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(532mg, 1.33mmol, 72%) was obtained.

[630] ^{1}H-NMR(400㎒, DMSO, δ) = 2.73 (brs, 2H), 3.04 (brs, 2H), 3.45 (brs, 2H), 3.73 (brs, 2H), 6.09 (m, 3H), 6.86 (m, 1H), 7.41 (s, 2H), 7.44 (m, 3H), 7.54 (m, 1H)

[631]

[632] Example 59

[633] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone

[634] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(577mg, 1.35mmol, 73%) was obtained.

[635] ^{1}H-NMR(400㎒, DMSO, δ) = 2.98 (brs, 4H), 3.43 (brs, 4H), 6.86 (t, 1H), 7.10 (d, 1H), 7.40 (s, 2H), 7.50 (m, 5H)

[636]

[637] Example 60

[638] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[639] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(516mg, 1.25mmol, 68%) was obtained.

[640] ^{1}H-NMR(400㎒, DMSO, δ) = 2.88 (brs, 4H), 3.43 (brs, 4H), 3.71 (s, 3H), 6.38 (m, 2H), 6.46 (dd, 1H), 7.10 (m, 1H), 7.38 (s, 2H), 7.51 (m, 4H)

[641]

[642] Example 61

[643] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[644] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine (354mg, 1.84mmol), a white solid required compound(523mg, 1.27mmol, 69%) was obtained.

[645] ^{1}H-NMR(400㎒, DMSO, δ) = 2.66 (brs, 4H), 3.40 (brs, 4H), 3.76 (s, 3H), 6.76 (d, 1H), 6.85 (t, 1H), 6.95 (m, 2H), 7.38 (s, 2H), 7.50 (m, 3H), 7.57 (m, 1H)

[646]

[647] Example 62

[648] synthesis of

(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[649] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a white solid required compound(633mg, 1.40mmol, 76%) was obtained.

[650] ^{1}H-NMR(400㎒, DMSO, δ) = 2.61 (brs, 2H), 3.14 (brs, 2H), 3.35 (brs, 2H), 7.15 (m, 2H), 7.17 (d, 1H), 7.46 (m, 1H), 7.39 (s, 2H), 7.54 (m, 3H), 7.59 (m, 1H)

[651]

[652] Example 63

[653] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[654] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(504mg, 1.26mmol, 69%) was obtained.

[655] ^{1}H-NMR(400㎒, DMSO, δ) = 2.62 (brs, 2H), 3.09 (brs, 2H), 3.31 (brs, 2H), 3.95 (brs, 2H), 6.80 (m, 4H), 7.31 (s, 2H), 7.50 (m, 3H), 7.53 (m, 1H)

[656]

[657] Example 64

[658] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[659] In a similar manner as described in Example 1, by using dimethylformimide (15mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol), hydroxybenzotriazole (299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(518mg, 1.30mmol, 71%) was obtained.

[660] ^{1}H-NMR(400㎒, DMSO, δ) = 2.60 (brs, 2H), 3.04 (brs, 2H), 3.32 (brs, 2H), 3.99 (brs, 2H), 6.87 (m, 1H), 7.00 (m, 2H), 7.19 (m, 1H), 7.41 (s, 2H), 7.54 (m, 3H), 7.56 (m, 1H)

[661]

[662] Example 65

[663] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methano

ne

[664] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid (440mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(561mg, 1.40mmol, 76%) was obtained.

[665] ^{1}H-NMR(400㎒, DMSO, δ) = 2.84 (brs, 4H), 3.45 (brs, 4H), 6.91 (m, 2H), 7.03(m, 2H), 7.36 (s, 2H), 7.52 (m, 3H), 7.59 (m, 1H)

[666]

[667] Example 66

[668] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[669] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid (409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine (332mg, 1.84mmol), a white solid required compound(508mg, 1.32mmol, 72%) was obtained.

[670] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.72 (brs, 2H), 3.04 (brs, 2H), 3.39 (brs, 2H), 3.69 (brs, 2H), 6.05 (m, 3H), 6.83 (t, 1H), 7.26 (m, 1H), 7.35 (brs, 2H), 7.45 (m, 3H)

[671]

[672] Example 67

[673] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone

[674] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid (409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(596mg, 1.37mmol, 74%) was obtained.

[675] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.73 (brs, 2H), 3.02 (brs, 2H), 3.39 (brs, 2H), 3.69 (brs, 2H), 6.65 (dd, 1H), 6.87 (d, 1H), 7.20 (m, 1H), 7.21 (m, 1H), 7.36 (brs, 2H), 7.43 (m, 3H)

[676]

[677] Example 68

[678] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[679] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(601mg, 1.52mmol, 82%) was obtained.

[680] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.61 (brs, 2H), 3.14 (brs, 2H), 3.30 (brs, 2H), 3.78 (brs, 2H), 3.80 (s, 3H), 6.42 (brs, 1H), 6.53 (m, 2H), 7.19 (m, 1H), 7.37 (brs, 2H), 7.43 (m, 3H), 7.46 (dd, 1H), 7.76 (dd, 1H)

[681] Example 69

[682] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[683] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(482mg, 1.21mmol, 66%) was obtained.

[684] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.63 (brs, 2H), 3.02 (brs, 2H), 3.36 (brs, 2H), 3.76 (brs, 2H), 3.89 (brs, 2H), 6.75 (brs, 1H), 6.89 (m, 1H), 6.90 (m, 1H), 7.24 (m, 1H), 7.33 (brs, 2H), 7.45 (m, 3H), 7.65 (dd, 1H)

[685] Example 70

[686] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[687] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-trifluoromethyl)phenyl)piperazine(424mg, 1.84mmol), a white solid required compound(639mg, 1.47mmol, 80%) was obtained.

[688] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.61 (brs, 2H), 3.17 (brs, 2H), 3.35 (brs, 2H), 7.01 (m, 2H), 7.15 (d, 1H), 7.21 (m, 1H), 7.39 (brs, 2H), 7.42 (m, 3H), 7.45 (m, 1H)

[689]

[690] Example 71

[691] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[692] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol),

1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(483mg, 1.26mmol, 68%) was obtained.

[693] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.60 (brs, 2H), 3.14 (brs, 2H), 3.36 (brs, 2H), 3.99 (brs, 2H), 6.83 (m, 4H), 7.20 (m, 1H), 7.39 (brs, 2H), 7.45 (m, 3H)

[694]

[695] Example 72

[696] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[697] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(312mg, 1.84mmol), a white solid required compound(381mg, 0.81mmol, 44%) was obtained.

[698] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.61 (brs, 2H), 3.06 (brs, 2H), 3.42 (brs, 2H), 4.02 (brs, 2H), 6.89 (m, 1H), 7.06 (m, 1H), 7.24 (m, 2H), 7.41 (brs, 2H), 7.48 (m, 3H)

[699]

[700] Example 73

[701] synthesis of (5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[702] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(576mg, 1.50mmol, 81%) was obtained.

[703] ^{1}H-NMR (400MHz, DMSO, δ) = 2.91 (brs, 4H), 3.50 (brs, 4H), 6.97 (m, 2H), 7.10 (m, 2H), 7.28 (m, 1H), 7.37 (brs, 2H), 7.46 (m, 3H)

[704]

[705] Example 74

[706] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[707] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required

compound(533mg, 1.39mmol, 75%) was obtained.

[708] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.69 (brs, 2H), 2.92 (brs, 2H), 3.40 (brs, 2H), 3.85 (brs, 2H), 6.62 (m, 1H), 6.78 (m, 1H), 7.06 (m, 2H), 7.27 (m, 1H), 7.37 (brs, 2H), 7.47 (m, 1H), 7.56 (m, 2H)

[709]

[710] Example 75

[711] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone

[712] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(613mg, 1.49mmol, 81%) was obtained.

[713] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.63 (brs, 2H), 3.09 (brs, 2H), 3.22 (brs, 2H), 3.87 (brs, 2H), 6.66 (dd, 1H), 6.87 (d, 1H), 7.28 (m, 1H), 7.36 (s, 2H), 7.37 (m, 1H), 7.48 (m, 1H), 7.57 (m, 2H)

[714]

[715] Example 76

[716] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[717] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(558mg, 1.41mmol, 77%) was obtained.

[718] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.64 (brs, 2H), 3.19 (brs, 2H), 3.30 (brs, 2H), 3.80 (s, 3H), 3.93 (brs, 2H), 6.42 (m, 1H), 6.48 (m, 2H), 7.13 (m, 1H), 7.26 (m, 1H), 7.36 (brs, 2H), 7.47 (m, 1H), 7.61 (m, 2H)

[719]

[720] Example 77

[721] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[722] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and

1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(464mg, 1.170.64mmol, 77%) was obtained.

[723] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.57 (brs, 2H), 3.03 (brs, 2H), 3.32 (brs, 2H), 3.83 (s, 3H), 3.95 (brs, 2H), 6.55 (m, 1H), 6.90 (m, 2H), 7.04 (m, 1H), 7.25 (m, 1H), 7.37 (brs, 2H), 7.45 (m, 1H), 7.59 (m, 2H)

[724] Example 78

[725] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[726] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-trifluoromethyl)phenyl)piperazine(424mg, 1.84mmol), a white solid required compound(596mg, 1.37mmol, 75%) was obtained.

[727] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.62 (brs, 2H), 3.07 (brs, 2H), 3.33 (brs, 2H), 3.90 (brs, 2H), 7.00 (m, 1H), 7.24 (m, 4H), 7.32 (brs, 2H), 7.44 (m, 1H), 7.59 (m, 2H)

[728]

[729] Example 79

[730] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[731] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(412mg, 1.08mmol, 59%) was obtained.

[732] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.61 (brs, 2H), 3.07 (brs, 2H), 3.32 (brs, 2H), 3.95 (brs, 2H), 6.77 (m, 4H), 7.22 (m, 1H), 7.33 (brs, 2H), 7.50 (m, 1H), 7.63 (m, 2H)

[733]

[734] Example 80

[735] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[736] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(439mg, 1.15mmol, 62%) was obtained.

[737] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 2.62 (brs, 2H), 3.02 (brs, 2H), 3.38 (brs, 2H), 4.01 (brs, 2H), 6.60 (m, 1H), 6.83 (m, 3H), 7.25 (m, 1H), 7.33 (brs, 2H), 7.47 (m, 1H), 7.63 (m, 2H)

[738]

[739] Example 81

[740] synthesis of (5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[741] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(538mg, 1.40mmol, 76%) was obtained.

[742] ^{1}H-NMR (400MHz, DMSO, δ) = 2.89 (brs, 4H), 3.49 (brs, 4H), 6.92 (m, 2H), 7.06 (m, 2H), 7.31 (m, 2H), 7.33 (brs, 2H), 7.54 (m, 2H)

[743]

[744] Example 82

[745] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[746] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(576mg, 1.28mmol, 70%) was obtained.

[747] ^{1}H-NMR(400㎒, DMSO, δ) = 2.71 (brs, 2H), 3.04 (brs, 2H), 3.43 (brs, 2H), 3.69 (brs, 2H), 6.07 (m, 3H), 6.79 (t, 1H), 7.31 (brs, 2H), 7.41 (m, 3H), 7.54 (m, 1H)

[748]

[749] Example 83

[750] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(3,4-dichlorophenyl)piperazine-1-yl)methanone

[751] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(713mg, 1.42mmol, 77%) was obtained.

[752] ^{1}H-NMR(400㎒, DMSO, δ) = 2.73 (brs, 2H), 3.03 (brs, 2H), 3.45 (brs, 2H), 3.71

(brs, 2H), 6.65 (dd, 1H), 6.87 (d, 1H), 7.29 (m, 1H), 7.31 (brs, 2H), 7.41 (m, 3H), 7.54 (m, 1H)

[753]

[754] Example 84

[755] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[756] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(592mg, 1.28mmol, 70%) was obtained.

[757] ^{1}H-NMR(400㎒, DMSO, δ) = 2.65 (brs, 2H), 3.12 (brs, 2H), 3.31 (brs, 2H), 3.79 (brs, 2H), 3.81 (s, 3H), 6.40 (brs, 1H), 6.50 (m, 2H), 7.32 (brs, 2H), 7.45 (m, 3H), 7.44 (dd, 1H), 7.59 (m, 1H), 7.77 (dd, 1H)

[758]

[759] Example 85

[760] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[761] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(559mg, 1.21mmol, 66%) was obtained.

[762] ^{1}H-NMR(400㎒, DMSO, δ) = 2.62 (brs, 2H), 2.95 (brs, 2H), 3.31 (brs, 2H), 3.75 (brs, 2H), 3.89 (s, 3H), 6.78 (brs, 1H), 6.86 (t, 1H), 6.91 (t, 1H), 7.32 (brs, 2H), 7.41 (m, 3H), 7.54 (m, 1H), 7.69 (dd, 1H)

[763]

[764] Example 86

[765] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[766] In a similar manner as described in Example 1, by using dichloromethane (30mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid (530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine (424mg, 1.84mmol), a white solid required compound(633mg, 1.27mmol, 69%) was obtained.

[767] ^{1}H-NMR(400㎒, DMSO, δ) = 2.61 (brs, 2H), 3.13 (brs, 2H), 3.35 (brs, 2H), 7.01 (m, 2H), 7.15 (d, 1H), 7.31 (brs, 2H), 7.45 (m, 4H), 7.58 (m, 1H)

[768]

[769] Example 87

[770] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[771] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(608mg, 1.36mmol, 73%) was obtained.

[772] ^{1}H-NMR(400㎒, DMSO, δ) = 2.60 (brs, 2H), 3.34 (brs, 2H), 3.29 (brs, 2H), 3.98 (brs, 2H), 6.71 (m, 4H), 7.31 (brs, 2H), 7.45 (m, 3H), 7.55 (m, 1H)

[773]

[774] Example 88

[775] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[776] In a similar manner as described in Example 1, by using dimethylformimide(15mL),5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(551mg, 1.23mmol, 67%) was obtained.

[777] ^{1}H-NMR(400㎒, DMSO, δ) = 2.63 (brs, 2H), 3.04 (brs, 2H), 3.33 (brs, 2H), 4.03 (brs, 2H), 6.85 (m, 1H), 7.04 (m, 2H), 7.20 (m, 1H), 7.30 (brs, 2H), 7.47 (m, 3H), 7.61 (m, 1H)

[778]

[779] Example 89

[780] synthesis of (5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[781] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid

required compound(607mg, 1.35mmol, 73%) was obtained.

[782] ^{1}H-NMR(400㎒, DMSO, δ) = 2.87 (brs, 4H), 3.47 (brs, 4H), 6.91 (m, 2H), 7.05 (m, 2H), 7.31 (brs, 2H), 7.44 (m, 3H), 7.62 (m, 1H)

[783]

[784] Example 90

[785] synthesis of (5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[786] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(573mg, 1.32mmol, 72%) was obtained.

[787] ^{1}H-NMR(400㎒, DMSO, δ) = 2.72 (brs, 2H), 3.06 (brs, 2H), 3.39 (brs, 2H), 3.69 (brs, 2H), 6.04 (m, 3H), 6.83 (m, 1H), 7.42 (brs, 2H), 7.40 (m, 1H), 7.75 (m, 2H), 7.79 (m, 1H)

[788]

[789] Example 91

[790] synthesis of (5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone

[791] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(633mg, 1.30mmol, 71%) was obtained.

[792] ^{1}H-NMR(400㎒, DMSO, δ) = 2.72 (brs, 2H), 3.09 (brs (brs, 2H), 3.38 (brs, 2H), 3.76 (brs, 2H), 6.66 (dd, 1H), 6.84 (d, 1H), 7.28 (m, 1H), 7.41 (brs, 2H), 7.40 (m, 1H), 7.73 (m, 2H), 7.78 (m, 1H)

[793]

[794] Example 92

[795] synthesis of (5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[796] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required

compound(549mg, 1.23mmol, 67%) was obtained.

[797] ^{1}H-NMR(400㎒, DMSO, δ) = 2.62 (brs, 2H), 3.15 (brs, 2H), 3.33 (brs, 2H), 3.81 (brs, 2H), 3.87 (s, 3H), 6.43 (s, 1H), 6.51 (m, 2H), 7.40 (m, 1H), 7.43 (brs, 2H), 7.44 (dd, 1H), 7.73 (m, 2H), 7.79 (dd, 1H)

[798]

[799] Example 93

[800] synthesis of (5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[801] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(473mg, 1.06mmol, 58%) was obtained.

[802] ^{1}H-NMR(400㎒, DMSO, δ) = 2.61 (brs, 2H), 3.02 (brs, 2H), 3.34 (brs, 2H), 3.75 (brs, 2H), 3.83 (s, 3H), 6.72 (brs, 1H), 6.89 (t, 1H), 6.92 (t, 1H), 7.43 (brs, 2H), 7.44 (m, 1H), 7.65 (dd, 1H), 7.72 (m, 2H), 7.75 (m, 1H)

[803]

[804] Example 94

[805] synthesis of 5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[806] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine(424mg, 1.84mmol), a white solid required compound(631mg, 1.30mmol, 71%) was obtained.

[807] ^{1}H-NMR(400㎒, DMSO, δ) = 2.65 (brs, 2H), 3.15 (brs, 4H), 3.37 (brs, 2H), 7.03 (m, 2H), 7.16 (d, 1H), 7.40 (m, 1H), 7.43 (brs, 2H), 7.44 (m, 1H), 7.70 (m, 2H), 7.76 (m, 1H)

[808]

[809] Example 95

[810] synthesis of (5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[811] In a similar manner as described in Example 1, by using dimethylformamide(15mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hy-

droxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(434mg, 1.00mmol, 55%) was obtained.

[812] ^{1}H-NMR(400㎒, DMSO, δ) = 2.61 (brs, 2H), 3.04 (brs, 2H), 3.32 (brs, 2H), 3.89 (brs, 2H), 6.79 (m, 4H), 7.38 (m, 1H), 7.46 (brs, 2H), 7.70 (m, 2H), 7.76 (m, 1H)

[813]

[814] Example 96

[815] synthesis of 5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[816] In a similar manner as described in Example 1, by using dimethylformamide(15mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(471mg, 1.09mmol, 59%) was obtained.

[817] ^{1}H-NMR(400㎒, DMSO, δ) = 2.63 (brs, 2H), 3.01 (brs, 2H), 3.35 (brs, 2H), 4.09 (brs, 2H), 6.81 (m, 1H), 7.06 (m, 2H), 7.19 (m, 1H), 7.42 (brs, 2H), 7.48 (m, 1H), 7.73 (m, 2H), 7.78 (m, 1H)

[818]

[819] Example 97

[820] synthesis of (5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[821] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(603mg, 1.39mmol, 75%) was obtained.

[822] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.86 (brs, 4H), 3.47 (brs, 4H), 6.90 (m, 2H), 7.04 (m, 2H), 7.43 (brs, 2H), 7.49 (m, 1H), 7.70 (m, 2H), 7.76 (m, 1H)

[823]

[824] Example 98

[825] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[826] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid

required compound(533mg, 1.18mmol, 64%) was obtained.

[827] ^{1}H-NMR(400㎒, DMSO, δ) = 2.72 (brs, 2H), 3.03 (brs, 2H), 3.43 (brs, 2H), 3.70 (brs, 2H), 6.08 (m, 3H), 6.79 (t, 1H), 7.31 (brs, 2H), 7.38 (d, 2H), 7.44 (d, 2H)

[828]

[829] Example 99

[830] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(3,4-dichlorophenyl)piperazine-1-yl)methanone

[831] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(688mg, 1.37mmol, 75%) was obtained.

[832] ^{1}H-NMR(400㎒, DMSO, δ) = 2.72 (brs, 2H), 3.03 (brs, 2H), 3.47 (brs, 2H), 3.71 (brs, 2H), 6.64 (dd, 1H), 6.86(d, 1H), 7.32 (brs, 2H), 7.33 (d, 2H), 7.45 (d, 2H), 7.54 (m, 1H)

[833]

[834] Example 100

[835] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[836] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(588mg, 1.27mmol, 69%) was obtained.

[837] ^{1}H-NMR(400㎒, DMSO, δ) = 2.65 (brs, 2H), 3.12 (brs, 2H), 3.31 (brs, 2H), 3.79 (brs, 2H), 3.81 (s, 3H), 6.40 (brs, 1H), 6.50 (m, 2H), 7.30 (brs, 2H), 7.36 (d, 2H), 7.44 (dd, 1H), 7.49 (d, 2H), 7.77 (dd, 1H)

[838]

[839] Example 101

[840] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[841] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid

required compound(603mg, 1.30mmol, 71%) was obtained.

[842] ^{1}H-NMR(400㎒, DMSO, δ) = 2.62 (brs,2H), 2.95 (brs, 2H), 3.31 (brs, 2H), 3.75 (brs, 2H), 3.89 (s, 3H), 6.78 (brs, 1H), 6.86 (t, 1H), 6.91 (t, 1H), 7.32 (brs, 2H), 7.36 (d, 2H), 7.45 (d, 2H), 7.69 (dd, 1H)

[843]

[844] Example 102

[845] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[846] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine(424mg, 1.84mmol), a white solid required compound(597mg, 1.19mmol, 65%) was obtained.

[847] ^{1}H-NMR(400㎒, DMSO, δ) = 2.63 (brs, 2H), 3.12 (brs, 2H), 3.33 (brs, 2H), 7.02 (m, 2H), 7.14 (d, 1H), 7.33 (brs, 2H), 7.38 (d, 2H), 7.45 (m, 1H), 7.46 (d, 2H), 7.58 (m, 1H)

[848]

[849] Example 103

[850] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[851] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(566mg, 1.26mmol, 69%) was obtained.

[852] ^{1}H-NMR(400㎒, DMSO, δ) = 2.62 (brs, 2H), 3.29 (brs, 2H), 3.34 (brs, 2H), 3.94 (brs, 2H), 6.71 (m, 4H), 7.33 (brs, 2H), 7.37 (d, 2H), 7.42 (d, 2H)

[853]

[854] Example 104

[855] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[856] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg,

2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(591mg, 1.32mmol, 72%) was obtained.

[857] ^{1}H-NMR(400㎒, DMSO, δ) = 2.63 (brs, 2H), 3.04 (brs, 2H), 3.33 (brs, 2H), 4.03 (brs, 2H), 6.85 (m, 1H), 7.03 (m, 2H), 7.22 (m, 1H), 7.31 (brs, 2H), 7.38 (d, 2H), 7.46 (d, 2H)

[858]

[859] Example 105

[860] synthesis of (5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[861] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(621mg, 1.38mmol, 75%) was obtained.

[862] ^{1}H-NMR(400㎒, DMSO, δ) = 2.83 (brs, 4H), 3.47 (brs, 4H), 6.91 (m, 2H), 7.05 (m, 2H), 7.31 (brs, 2H), 7.36 (d, 2H), 7.46 (d, 2H)

[863]

[864] Example 106

[865] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[866] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(566mg, 1.31mmol, 71%) was obtained.

[867] ^{1}H-NMR(400㎒, DMSO, δ) = 2.73 (brs, 2H), 3.02 (brs, 2H), 3.31 (brs, 2H), 3.72 (brs, 2H), 6.14 (m, 3H), 6.87 (m, 1H), 7.29 (m, 1H), 7.49 (brs, 2H), 7.63 (m, 1H), 7.71 (m, 2H)

[868]

[869] Example 107

[870] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone

[871] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol),

1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(633mg, 1.30mmol, 71%) was obtained.

[872] ^{1}H-NMR(400㎒, DMSO, δ) = 2.73 (brs, 2H), 3.08 (brs (brs, 2H), 3.35 (brs, 2H), 3.72 (brs, 2H), 6.62 (dd, 1H), 6.84 (d, 1H), 7.24 (m, 1H), 7.31 (m, 1H), 7.44 (brs, 2H), 7.61 (m, 1H), 7.71 (m, 2H)

[873]

[874] Example 108

[875] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[876] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(549mg, 1.23mmol, 67%) was obtained.

[877] ^{1}H-NMR(400㎒, DMSO, δ) = 2.63 (brs, 2H), 3.18 (brs, 2H), 3.30 (brs, 2H), 3.82 (brs, 2H), 3.85 (s, 3H), 6.39 (s, 1H), 6.48 (m, 2H), 7.29 (m, 1H), 7.37 (m, 1H), 7.40 (brs, 2H), 7.60 (m, 1H), 7.69 (m, 2H)

[878]

[879] Example 109

[880] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[881] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(473mg, 1.06mmol, 58%) was obtained.

[882] ^{1}H-NMR(400㎒, DMSO, δ) = 2.63 (brs, 2H), 3.12 (brs, 2H), 3.37 (brs, 2H), 3.79 (brs, 2H), 3.81 (s, 3H), 6.74 (brs, 1H), 6.82 (t, 1H), 6.91 (t, 1H), 7.29 (m, 1H), 7.46 (m, 3H), 7.65 (m, 1H), 7.70 (m, 2H)

[883]

[884] Example 110

[885] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone

[886] In a similar manner as described in Example 1, by using dichloromethane(30mL),

5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine(424mg, 1.84mmol), a white solid required compound(631mg, 1.30mmol, 71%) was obtained.

[887] ^{1}H-NMR(400㎒, DMSO, δ) = 2.69 (brs, 2H), 3.14 (brs, 4H), 3.35 (brs, 2H), 7.01 (m, 2H), 7.21 (d, 1H), 7.33 (m, 1H), 7.41 (m, 1H), 7.45 (brs, 2H), 7.63 (m, 1H), 7.70 (m, 2H)

[888]

[889] Example 111

[890] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[891] In a similar manner as described in Example 1, by using dimethylformamide(15mL), 5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(460mg, 106mmol, 58%) was obtained.

[892] ^{1}H-NMR(400㎒, DMSO, δ) = 2.69 (brs, 4H), 3.82 (brs, 4H), 6.72 (m, 4H), 7.32 (m, 1H), 7.46 (brs, 2H), 7.64 (m, 1H), 7.73 (m, 1H)

[893]

[894] Example 112

[895] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[896] In a similar manner as described in Example 1, by using dimethylformamide(15mL), 5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(492mg, 1.14mmol, 62%) was obtained.

[897] ^{1}H-NMR(400㎒, DMSO, δ) = 2.62 (brs, 2H), 3.02 (brs, 2H), 3.32 (brs, 2H), 4.09 (brs, 2H), 6.85 (m, 1H), 7.12 (m, 2H), 7.17 (m, 1H), 7.29 (m, 1H), 7.46 (brs, 2H), 7.63 (m, 1H), 7.71 (m, 2H)

[898]

[899] Example 113

[900] synthesis of (5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[901] In a similar manner as described in Example 1, by using dichloromethane(30mL),

5-amino-3-(3-trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(603mg, 1.39mmol, 75%) was obtained.

[902] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 2.89 (brs, 4H), 3.46 (brs, 4H), 6.91 (m, 2H), 7.05 (m, 2H), 7.31 (m, 1H), 7.47 (brs, 2H), 7.60 (m, 1H), 7.76 (m, 2H)

[903]

[904] Example 114

[905] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone

[906] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(538mg, 1.19mmol, 65%) was obtained.

[907] ^{1}H-NMR(400㎒, DMSO, δ) = 2.74 (brs, 2H), 3.06 (brs, 2H), 3.41 (brs, 2H), 3.69 (brs, 2H), 6.12 (m, 3H), 6.78 (t, 1H), 7.33 (brs, 2H), 7.36 (m, 2H), 7.53 (m, 1H), 7.69 (m, 1H)

[908]

[909] Example 115

[910] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone

[911] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3,4-dichlorophenyl)piperazine(425mg, 1.84mmol), a white solid required compound(652mg, 1.31mmol, 71%) was obtained.

[912] ^{1}H-NMR(400㎒, DMSO, δ) = 2.75 (brs, 2H), 3.09 (brs, 2H), 3.51 (brs, 2H), 3.78 (brs, 2H), 6.60 (dd, 1H), 6.89 (d, 1H), 7.36 (m, 1H), 7.37 (brs, 2H), 7.53 (m, 3H), 7.69 (m, 1H)

[913]

[914] Example 116

[915] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone

[916] In a similar manner as described in Example 1, by using dichloromethane(30mL),

5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(562mg, 1.22mmol, 66%) was obtained.

[917] ^{1}H-NMR(400㎒, DMSO, δ) = 2.63 (brs, 2H), 3.15 (brs, 2H), 3.29 (brs, 2H), 3.82 (brs, 2H), 3.82 (s, 3H), 6.43 (brs, 1H), 6.52 (m, 2H), 7.31 (brs, 2H), 7.36 (m, 2H), 7.51(m, 1H), 7.70(m, 1H), 7.77 (dd, 1H)

[918]

[919] Example 117

[920] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone

[921] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(2-methoxyphenyl)piperazine(354mg, 1.84mmol), a white solid required compound(622mg, 1.35mmol, 73%) was obtained.

[922] ^{1}H-NMR(400㎒, DMSO, δ) = 2.60 (brs, 2H), 2.99 (brs, 2H), 3.29 (brs, 2H), 3.74 (brs, 2H), 3.85 (s, 3H), 6.71 (brs, 1H), 6.85 (t, 1H), 6.93 (t, 1H), 7.31 (brs, 2H), 7.36 (m, 2H), 7.53 (m, 1H), 7.65 (m, 1H), 7.69 (dd, 1H)

[923]

[924] Example 118

[925] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-trifluoromethyl)phenyl)piperazine-1-yl)methanone

[926] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(3-(trifluoromethyl)phenyl)piperazine(424mg, 1.84mmol), a white solid required compound(542mg, 1.19mmol, 59%) was obtained.

[927] ^{1}H-NMR(400㎒, DMSO, δ) = 2.60 (brs, 2H), 3.10 (brs, 2H), 3.35 (brs, 2H), 7.01 (m, 2H), 7.15 (d, 1H), 7.31 (brs, 2H), 7.36 (m, 2H), 7.43 (m, 1H), 7.51 (m, 1H), 7.53 (m, 1H), 7.65 (m, 1H)

[928]

[929] Example 119

[930] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone

[931] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 4-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(601mg, 1.34mmol, 72%) was obtained.

[932] ^{1}H-NMR(400㎒, DMSO, δ) = 2.61 (brs, 2H), 3.31 (brs, 2H), 3.32 (brs, 2H), 3.95 (brs, 2H), 6.69 (m, 4H), 7.31 (brs, 2H), 7.38 (m, 2H), 7.52 (m, 1H), 7.72 (m, 1H)

[933]

[934] Example 120

[935] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone

[936] In a similar manner as described in Example 1, by using dimethylformimide(15mL), 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol), hydroxybenzotriazole(299mg, 2.21mmol) and 2-(piperazine-1-yl)phenol(328mg, 1.84mmol), a white solid required compound(588mg, 1.31mmol, 71%) was obtained.

[937] ^{1}H-NMR(400㎒, DMSO, δ) = 2.61 (brs, 2H), 3.06 (brs, 2H), 3.31 (brs, 2H), 4.02 (brs, 2H), 6.84 (m, 1H), 7.01 (m, 2H), 7.23 (m, 1H), 7.31 (brs, 2H), 7.38 (m, 2H), 7.54 (m, 1H), 7.66 (m, 1H)

[938]

[939] Example 121

[940] synthesis of (5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone

[941] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and 1-(4-fluorophenyl)piperazine(332mg, 1.84mmol), a white solid required compound(609mg, 1.35mmol, 73%) was obtained.

[942] ^{1}H-NMR(400㎒, DMSO, δ) = 2.81 (brs, 4H), 3.45 (brs, 4H), 6.92 (m, 2H), 7.09 (m, 2H), 7.34 (brs, 2H), 7.39 (m, 2H), 7.51 (m, 1H), 7.68 (m, 1H)

[943]

[944] Example 122

[945] synthesis of ethyl-1-(5-amino-3-(2-chlorophenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate

[946] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-chlorophenyl)isoxazol-4-carboxylic acid(439mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and ethyl piperazine-4-carboxylate(289mg, 1.84mmol), a white solid required compound(422mg, 1.12mmol, 60%) was obtained.

[947] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 1.14 (m, 5H), 1.66 (m, 2H), 2.51 (m, 1H), 2.81 (q, 2H), 3.76 (d, 2H), 4.05 (q, 2H), 7.25 (s, 2H), 7.46 (m, 3H), 7.57 (m, 1H)

[948]

[949] Example 123

[950] synthesis of methyl-1-(5-amino-3-(2-fluorophenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate

[951] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-fluorophenyl)isoxazol-4-carboxylic acid(409mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and methyl piperazine-4-carboxylate (263mg, 1.84mmol), a white solid required compound(463mg, 1.33mmol, 72%) was obtained.

[952] ^{1}H-NMR (400MHz, $CDCl_3$, δ) = 1.58 (m, 2H), 1.81 (m, 2H), 2.03 (m, 2H), 2.29 (m, 1H), 7.76 (m, 2H), 3.71 (s, 3H), 7.26 (m, 1H), 7.45 (m, 1H), 7.64 (m, 2H)

[953]

[954] Example 124

[955] synthesis of ethyl-1-(5-amino-3-(2-trifluoromethoxy)phenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate

[956] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carboxylic acid(530mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and ethyl piperazine-4-carboxylate(289mg, 1.84mmol), a white solid required compound(429mg, 1.00mmol, 55%) was obtained.

[957] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 1.16 (m, 5H), 1.65 (m, 2H), 2.54 (m, 1H), 2.83 (q, 2H), 3.74 (d, 2H), 4.06 (q, 2H), 7.41, (brs, 2H), 7.45 (m, 3H), 7.59 (m, 1H)

[958]

[959] Example 125

[960] synthesis of ethyl-1-(5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate

[961] In a similar manner as described in Example 1, by using dichloromethane(30mL), 5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carboxylic acid(501mg, 1.84mmol), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride(388mg, 2.02mmol) and ethyl piperazine-4-carboxylate(289mg, 1.84mmol), a white solid required

compound(495mg, 1.20mmol, 65%) was obtained.

[962] ^{1}H-NMR(400㎒, $CDCl_3$, δ) = 1.13 (m, 5H), 1.62 (m, 2H), 2.49 (m, 1H), 2.76 (q, 2H), 3.74 (d, 2H), 4.09 (q, 2H), 7.41 (m, 1H), 7.43 (brs, 2H), 7.78 (m, 2H), 7.81 (m, 1H)

[963]

[964] Example 126

[965] synthesis of (4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone hydrochloric acid

[966] (4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone (100mg, 0.20mmol) was dissolved in acetone (10mL), cooled to 0℃ and slowly added with hydrochloric ethanol (10%, 73mg, 0.20mmol). The resultant product was stirred at room temperature for 8 hours, filtered, and dried so as to provide a white solid required compound (84mg, 1.20mmol, 78%).

[967] ^{1}H-NMR(400㎒, DMSO, δ) = 2.55 (s, 3H), 2.78 (brs, 2H), 3.14 (brs, 2H), 3.28 (brs, 2H), 3.58 (brs, 2H), 6.88 (dd, 1H), 7.10 (d, 1H), 7.40 (d, 1H), 7.56 (m, 2H), 7.68 (m, 2H)

[968]

[969] Example 127

[970] synthesis of (3-(2-chlorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone hydrochloric acid

[971] In a similar manner as described in Example 126, by using acetone(10mL), 3-(2-chlorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone(82mg, 0.20mmol) and hydrochloric ethanol(10%, 73mg, 0.20mmol), a white solid required compound(58mg, 0.13, 65%) was obtained.

[972] ^{1}H-NMR(400㎒, DMSO, δ) = 2.56 (s, 3H), 2.74 (brs, 2H), 3.06 (brs, 2H), 3.53 (brs, 2H), 3.72 (brs, 2H), 3.74 (s, 3H), 6.66 (m, 1H), 7.12 (m, 2H), 7.52 (m, 4H), 7.66 (m, 1H)

[973]

[974] Example 128

[975] synthesis of ethyl-1-(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carbomyl)piperazine-4-carboxylate hydrochloric acid

[976] In a similar manner as described in Example 126, by using acetone(10mL), ethyl-1-(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-carbomyl)piperazine-4-carboxylate(85mg, 0.20mmol) and hydrochloric ethanol(10%, 73mg, 0.20mmol), a white solid required compound(64mg, 0.14mmol, 69%) was obtained.

[977] ^{1}H-NMR(400㎒, DMSO, δ) = 1.18 (m, 5H), 1.70 (m, 2H), 2.53 (m, 1H), 2.82 (q,

2H), 3.70 (d, 2H), 4.18 (q, 2H), 7.42 (m, 3H), 7.63 (brs, 2H), 7.72 (m, 1H)

[978]

[979] Example 129

[980] synthesis of (4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone hydrochloric acid

[981] In a similar manner as described in Example 126, by using acetone(10mL), (4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone(90mg, 0.20mmol) and hydrochloric ethanol(10%, 73mg, 0.20mmol), a white solid required compound(53mg, 0.11mmol, 55%) was obtained.

[982] ^{1}H-NMR(400㎒, DMSO, δ) = 2.36 (brs, 2H), 2.57 (s, 3H), 2.87 (brs, 2H), 3.31 (brs, 2H), 3.74 (brs, 2H), 3.82 (s, 3H), 6.39 (m, 2H), 7.12 (m, 2H), 7.71 (m, 2H), 7.87 (m, 1H)

[983]

[984] Example 130

[985] synthesis of (3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone hydrochloric acid

[986] In a similar manner as described in Example 126, by using acetone(10mL), 3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone(76mg, 0.20mmol) and hydrochloric ethanol(10%, 73mg, 0.20mmol), a white solid required compound(48mg, 0.12mmol, 57%) was obtained.

[987] ^{1}H-NMR(400㎒, DMSO, δ) = 2.48 (brs, 2H), 2.53 (s, 3H), 2.86 (brs, 2H), 3.17 (brs, 2H), 3.84 (brs, 2H), 7.24 (m, 3H), 7.42 (m, 3H), 7.56 (m, 2H)

[988]

[989] Example 131

[990] synthesis of (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone hydrochloric acid

[991] In a similar manner as described in Example 126, by using acetone(10mL), (5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone(83mg, 0.20mmol) and hydrochloric ethanol(10%, 73mg, 0.20mmol), a white solid required compound(63mg, 0.14mmol, 70%) was obtained.

[992] ^{1}H-NMR(400㎒, DMSO, δ) = 2.58 (brs, 4H), 3.29 (brs, 2H), 3.53 (brs, 2H), 3.66 (s, 3H), 6.49 (m, 2H), 6.58 (m, 1H), 7.24 (m, 1H), 7.62 (s, 2H), 7.66 (m, 4H)

[993]

[994] Experimental Example 1: Reduction assay using GFP expression influenza virus

[995] Acell (MDCK) was infected with an influenza virus (K09) expressing GFP (Green

fluorescence protein) for 1 hour, and cultured in a medium added with a compound with different concentrations. After 24 to 72 hours, through a fluorescent microscope, a GFP signal was observed. Then, a cell not treated with a virus and a compound at all, and a cell only infected with an influenza virus were used as control groups. If the compound has an antiviral effect, it can be observed that the GFP signal is decreased according to an increase of the concentration of the compound.

[996]

[997] Experimental Example 2: Virucidal assay by plaque reduction assay

[998] In this experiment, before a cell is infected with a virus, the virus is directly treated with a compound so as to determine if the compound has an effect on the inhibition of the intracellular penetration of the influenza virus. For this, first, a compound with different concentrations was reacted with an influenza virus at room temperature for 1hour. Then, an MDCK cell was infected with the virus for 1 hour, washed with PBS, and cultured in a medium including 2% oxoid agar. After 72 hours, the cell was dyed with crystal violet. Then, it was observed if a plaque was formed. At the positions added with the compound with different concentrations, the number and size of plaques were compared to those in the control groups. Then, through analysis of antiviral activity, EC50 was determined.

[999]

[1000] Experimental Example 3: cytotoxicity assay using MTT(3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl-2H-tetrazolium bromide)

[1001] In this experiment, a cell was infected with a virus, and then the virus was directly treated with a compound so as to determine if the virus-infected cell has toxicity. For this, a cell (MDCK) was infected with an influenza virus (K09) for 1 hour, and treated with the compound with different concentrations for 24 hours. Then, the cell was treated with a MTT reagent for 1 hour. After 1 hour, a formazan crystal produced by the MTT reagent was dissolved in DMSO, and the absorbance was measured by an ELISA reader so as to determine CC50.

[1002] The antiviral efficacy test of the inventive compound was carried out on compounds according to Examples of this specification through Experimental Example 1 to Experimental Example 3. As a result, it was found that the inventive compound has a Formula structure having antiviral activity.

[1003] From among compounds according to Examples of this specification, about 30 compounds were determined through reduction assay to show antiviral activity after intracellular infection of a virus.

[1004] These compounds were subjected to MTT assay, and reduction assay, and EC50, CC50, and SI (Selective index) values were measured. The results are noted in Table 1 below.

[1005] 1) EC50 (Effective Concentration 50%):

[1006] measured by reduction assay. A minimum concentration of the compound, at which the number of plaques is reduced to half or more compared to that of a control group

[1007] 2) CC50 (Cytotoxicity concentration 50%):

[1008] measured by MTT assay. A maximum concentration of the compound, at which the number of cells is reduced to half or more compared to that of a control group

[1009] 3) SI (Selective Index): value indicated by CC50/EC50

[1010]

[1011] Table 1

[Table 1]

		Reduction assay result		MTT assay (Experimental Example 3)	SI value
		GFP reduction (Experimental Example 1)	Plaque reduction (Experimental Example 2)		
		effect	EC50(μg/ml)	CC50(μg/ml)	K09
Control	**Oseltamivir**	X	0.3905	625 to 1250	1600.51 to 3201.024
1	Example 3	O	0.33 to 0.65	308 to 628	473.84 to 1903.03
2	Example 4	O	12.5 to 25	78.12 to 156.25	3.125 to 12.5
3	Example 9	O	0.195 to 0.39	312.5 to 625	801.282 to 3205.128
4	Example 11	O	〈0.16	287 to 625	〉1793 or 〉3906
5	Example 12	O	3.125	78.125 to 156.25	25 to 50
6	Example 16	O	0.39	78.12	200.321
7	Example 27	O	2.4 to 3.9	9.77 to 19.53	2.5 to 8.13
8	Example 35	O	0.395 to 0.781	312.5 to 625	400.128 to 1582.278
9	Example 36	O	1.56	500〈	320〈
10	Example 43	X	X	2500	X
11	Example 51	O	2.4 to 3.9	15.25 to 25.92	3.91 to 10.80
12	Example 53	O	3.12	500〈	160〈
13	Example 60	O	0.1952	500〈	2560.82〈
14	Example 61	O	0.39	62.5 to 125	159.94 to 319.89
15	Example 67	O	2.4 to 3.9	10.12 to 21.25	2.59 to 8.85
16	Example 68	O	17.5 to 29	88.12 to 136.75	3.03 to 7.81
17	Example 72	O	25 to 50	15.62 to 31.25	0.31 to 1.25
18	Example 75	O	50〈	625 to 1250	12.5 to 25.0
19	Example 83	O	0.65 to 1.5	150.3 to 189.64	100.2 to 291.75
20	Example 91	O	12.45 to 25.80	18.35 to 29.87	0.71 to 2.39
21	Example 92	O	21 to 45	14.62 to 33.52	0.32 to 1.59
22	Example 99	O	21 to 45	14.62 to 33.52	0.32 to 1.59
23	Example 100	O	29 to 37	18.45 to 46.53	0.49 to 12.57

[1012]

24	Example 107	O	2.72 to 3.9	122.25 to 170.50	31.34 to 62.68
25	Example 109	O	1.52 to 3.5	147.25 to 190.64	42.07 to 125.4
26	Example 112	O	25 to 50	16.5 to 34.27	0.33 to 1.37
27	Example 115	O	21 to 45	15.5 to 35.75	0.34 to 1.70
28	Example 116	O	15 to 32	13.65 to 25.64	0.42 to 1.70
29	Example 122	O	4.5 to 8.5	160.59 to 320.75	18.89 to 71.27
30	Example 124	O	3.125 to 6.25	312.5	50 to 100

[1013] * O=effective, X=ineffective.

[1014]

[1015] From among the compounds according to Examples of this specification, some compounds showing a high antiviral activity effect, from Example 3, Example 4, Example 9, Example 11, Example 12, Example 16, Example 35, Example 60 and Example 124, were subjected to antiviral drug efficacy assay of novel influenza virus (K09 and B/Field), H1N1 influenza virus (solomon) and Oseltamivir resistant strain virus, according to the method of Experimental Examples 2 and 3. The results are noted in Table 2 below.

[1016]

[1017] Table 2

[Table 2]

Oseltamivir	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	0.3905	625 to 1250	1600.512 to 3201.024
B/Field	6.25		200 to 100
Solomon	3.125 to 6.25		100 to 400
Oseltamivir resistant strain	50		12.5 to 25
Example 3	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	0.33 to 0.65	308 to 628	473.84 to 1903.03
B/Field	50 〈		6.16〉 or 12.56〉
Solomon	0.064 to 0.094		3276.59 to 9812.50
Oseltamivir resistant strain	0.064 to 0.094		3276.59 to 9812.50
Example 4	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	12.5 to 25	78.125 to 156.25	3.125 to 12.5
B/Field	50 〈		1.563〉
Solomon	12.5		6.25 to 12.5
Oseltamivir resistant strain	50		1.563 to 3.125
Example 9	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	0.195 to 0.39	312.5 to 625	801.282 to 3205.128
B/Field	50 〈		6.25〉 or 12.5〉
Solomon	0.048 to 0.097		3221.649 to 13020.833
Oseltamivir resistant strain	0.048 to 0.097		3221.649 to 13020.833
Example 11	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	〈0.16	287 to 625	〉1793 or 〉3906
B/Field	4.25		67.529 to 147.058
Solomon	0.087 to 0.199		1442.211 to 7183.908
Oseltamivir resistant strain	0.195		1471.794 to 3205.128
Example 12	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	3.125	78.125 to 156.25	25 to 50
B/Field	50 〈		1.563〉 or 3.125〉
Solomon	0.781		100.032 to 200.064
Oseltamivir resistant strain	1.562		50.016 to 100.032
Example 16	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	0.39	78.125	200.321
B/Field	25		3.125
Solomon	0.097 to 0.195		400.641 to 805.412
Oseltamivir resistant strain	0.39 to 0.781		100.032 to 200.321
Example 35	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	0.395 to 0.781	312.5 to 625	400.128 to 1582.278
B/Field	6.25		50 to 100
Solomon	0.097 to 0.195		1602.564 to 6443.298
Oseltamivir resistant strain	0.195		1602.564 to 3205.128

[1018]

Example 60	EC50(μg/ml)	CC50(μg/ml)	SI value
K09	0.1952	500 〈	2560.82 〈
B/Field	6.25		80 〈
Solomon	0.053 to 0.094		5319.148 〈 or 9433.962 〈
Oseltamivir resistant strain	0.053 to 0.094		5319.148 〈 or 9433.962 〈
Example 124	**EC50(μg/ml)**	**CC50(μg/ml)**	**SI value**
K09	3.125 to 6.25	312.5	50 to 100
B/Field	50 〈		6.25〉
Solomon	6.25		50
Oseltamivir resistant strain	25		12.5

[1019]

[1020] As noted in Table 1, it can be seen from the results that the SI value obtained by EC50 and CC50 was the highest in the compounds from Example 11, Example 35 and Example 60. Especially, most of the compounds according to Examples of this specification showed a high effect in inhibition of propagation of an intracellular infected virus.

[1021] At present, Oseltamivir (tamiflu) and Zanamivir (relenza) used as an influenza virus therapeutic agent are drugs which inhibit Neuraminidase related to the release of an influenza virus, thereby inhibiting movement of the virus to non-infected cells. Also, as other therapeutic agents, M2 ion channel inhibitors of an influenza virus such as Amantadine and Rimantadine are used. However, at present, from some research results, it has been reported that a mutant influenza virus resistant to Oseltamivir was discovered. This is because the influenza virus is an RNA virus that can be more easily mutated than DNAviruses. Accordingly, as advents and side effects of a virus resistant to Oseltamivir have increased, it is urgently required to develop an effective novel influenza virus therapeutic agent.

[1022] Accordingly, compounds showing a high antiviral activity effect on a virus strain resistant to Oseltamivir (tamiflu), from Example 3, Example 4, Example 9, Example 11, Example 12, Example 16, Example 35, Example 60, and Example 124, and their derivatives are very useful drugs in the development of an effective novel influenza virus therapeutic agent.

[1023]

[1024] Experimental Example 4

[1025] An acute toxicitytest through oral administration in a rat

[1026] The acute toxicity of the inventive compound was determined through oral administration in a rat. Since the compound is expected to be orally administered in a clinical situation, an oral administration route was selected. A male rat aged 6 weeks

(SD-Rat, 220±30g) was subjected to quarantine, and acclimated for 1 week under a condition of lighting of 12 hours (08:00~20:00), and luminance of 150~300 Lux at 22±3℃ at a relative humidity of 50±20%, while being freely fed with feed and water. Each of a control group and an experimental group include 8 rats. The control group was orally administered with 0.5% HPMC, and the experimental group was orally administered with a material (different concentrations) suspended in 0.5% HPMC, by using a sonde in an amount in proportion to the measured weight of each individual.

[1027] The concentration of the drug administered to the experimental group was set as 2000mg/kg (the highest concentration for a single dose administration in a non-clinical test), and 1000mg/kg, and 500mg/kg (with a common ratio). For 14 days from drug administration, clinical symptoms were observed while the weight change was measured. Test animals that died during the test were subjected to autopsy, and abnormalities of main organs (heart, liver, lung, spleen, kidney, and large intestine) were observed and recorded. On the last day of the test (on the 14^{th} day from the administration), all individuals were subjected to autopsy, and the changes of the organs caused by a test material were observed and compared to those in the control group. In the control group, no rats had died, and abnormalities were not observed through autopsy.

[1028] Each group was orally administered in a concentration of 500mg/kg, 1000mg/kg, and 2000mg/kg. For 14 days from the administration, according to the test method, clinical symptoms were observed. On the last day of the test (on the 14^{th}day from the administration), changes of the organswere observed with a naked eye through autopsy. The control group, and experimental groups administered with 500mg/kg, 1000mg/kg, and 2000mg/kg did not show any premonitory symptoms right after administration. Also, in the groups administered in various amounts, no individuals died. Also, all administration groups showed a similar weight increase ratio irrespective of the amount of a drug during the observation period. Further, no abnormal responses were observed, and from the autopsy results, no peculiarities were observed. The results of this experiment are noted in Table 3, from which it was found that the compounds of Examples have an LD50 value of 2000mg/kg or more in oral administration. From this result, it can be determined that the inventive compound is a safe material in view of acute toxicity.

[1029]

[1030] Table 3

[Table 3]

	Example No.	LD50
Control	Oseltamivir	2,000 〈
1	3	2,000 〈
2	4	2,000 〈
3	9	2,000 〈
4	11	2,000 〈
5	12	2,000 〈
6	16	2,000 〈
7	27	2,000 〈
8	35	2,000 〈
9	60	2,000 〈
10	61	2,000 〈
11	83	2,000 〈
12	107	2,000 〈
13	109	2,000 〈
14	122	2,000 〈
15	124	2,000 〈

[1031]

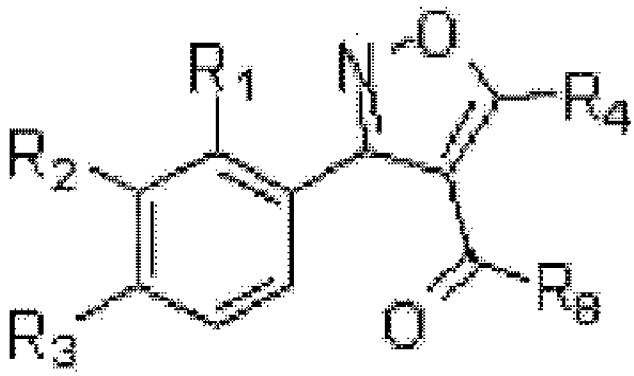
Industrial Applicability

[1032] Although several exemplary embodiments of the present invention have been described for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

Claims

[Claim 1] A compound represented by Formula 1 below, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite:

Formula 1



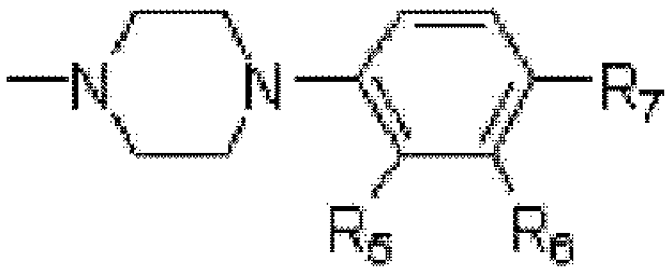
wherein in Formula 1,

R_1, R_2 and R_3 each independently represents hydrogen, lower alkyl optionally substituted with halogen, lower alkoxy optionally substituted with halogen, or halogen,

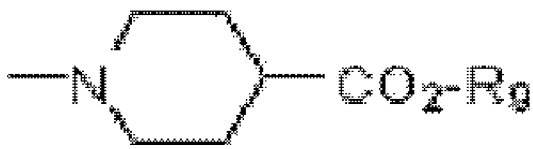
R_4 represents methyl or amine, and

R_8 is substituted with a radical of Formula 2 below, or substituted with a radical of Formula 3 below,

Formula 2



Formula 3



wherein, R_5, R_6 and R_7 each independently represents hydrogen, lower alkyl optionally substituted with halogen, hydroxy, lower alkoxy, or halogen, and

R_9 represents lower alkyl.

[Claim 2] The compound or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, as claimed in claim 1, wherein when the radical of Formula 2 is substituted for R_8,

two from among R_1, R_2 and R_3 represent hydrogen, the remaining one

represents lower alkyl optionally substituted with halogen, lower alkoxy optionally substituted with halogen, or halogen, preferably fluoro or chlorine, R_4 represents methyl, or amine, and from among R_5, R_6 and R_7, one or two each independently represents hydrogen, lower alkyl optionally substituted with halogen, hydroxy, lower alkoxy, or halogen;

two from among R_1, R_2 and R_3 represent hydrogen, the remaining one represents trifluoromethyl, fluoro, or trifluoromethoxy, R_4 represents methyl or amine, and from among R_5, R_6 and R_7, one or two each independently represents hydrogen, methoxy, chlorine, fluoro, trifluoromethyl or hydroxy; or

R_1 represents halogen, preferably chlorine, R_4 represents methyl or amine, R_2, R_3, R_5, and R_7 each represents hydrogen, and R_6 represents alkoxy, preferably methoxy.

[Claim 3] The compound or itspharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, as claimed in claim 1, wherein when the radical of Formula 2 is substituted for R_8,

R_1 represents trifluoromethyl, or trifluoromethoxy, R_2 and R_3 represent hydrogen, R_4 represents methyl or amine, and from among R_5, R_6 and R_7, one or two each independently represents hydrogen, hydroxy, methoxy, or chlorine;

R_1 represents chlorine, R_4 represents methyl, R_2, R_3, R_5 and R_7 each represents hydrogen, and R_6 represents methoxy; or

R_2 represents fluoro, trifluoromethyl, or trifluoromethoxy, R_1 and R_3 each represents hydrogen, R_4 represents methyl or amine, and from among R_5, R_6 and R_7, one or two each independently represents hydrogen, hydroxy, methoxy, trifluoromethyl or chlorine.

[Claim 4] The compound or itspharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, as claimed in claim 1, wherein when the radical of Formula 3 is substituted for R_8,

two from among R_1, R_2 and R_3 represent hydrogen, the remaining one represents lower alkyl optionally substituted with halogen, lower alkoxy optionally substituted with halogen, or halogen, R_4 represents amine, and R_9 represents lower alkyl, or

R_4 represents amine, two from among R_1, R_2 and R_3 represent hydrogen, the remaining one represents trifluoromethyl, fluoro, or trifluoromethoxy, and R_9 represents methyl or ethyl.

[Claim 5] The compound or itspharmaceutically acceptable salt, hydrate, solvate,

prodrug, or composite, as claimed in claim 1, wherein when the radical of Formula 3 is substituted for R_8, R_1 represents trifluoromethoxy, R_2 and R_3 each represents hydrogen, R_4 represents amine, and R_9 represents ethyl.

[Claim 6] The compound, or itspharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, as claimed in claim 1, wherein the compound comprises

(4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,

(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,

(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,

(4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)methanone,

(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,

(4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,

(4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,

(4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)methanone,

(3-(2-chlorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,

(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone,

(4-(3,4-dichlorophenyl)piperazine-1-yl)(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)methanone,

(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,

(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,

(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,

(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone,

(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-hydroxyphenyl)pipera

zine-1-yl)methanone,
(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone,
(4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(4-trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluorometho

xy)phenyl)isoxazol-4-yl)methanone,
(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(5-methyl-3-(3-trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(2-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-trifluoro

methyl)phenyl)piperazine-1-yl)methanone,
(4-(4-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(4-fluorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazin

e-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazin e-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piper azine-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)pipera zine-1-yl)methanone,
(amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazi ne-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)pheny l)piperazine-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperaz ine-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperaz ine-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazin e-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-fluorophe nyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(3,4-dichloroph enyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyp henyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-methoxyp henyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoro methyl)phenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-hydroxyp henyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-hydroxyp henyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-fluorophe nyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-fluoropheny l)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3,4-dichlorop henyl)piperazine-1-yl)methanone,
(5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-methoxyphe

nyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethylphenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-(trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-hydroxyphe

nyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-fluorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-trifluoromethyl)phenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(4-fluorophenyl)piperazine-1-yl)methanone, ethyl-
1-(5-amino-3-(2-chlorophenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate, methyl-
1-(5-amino-3-(2-fluorophenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate, ethyl-
1-(5-amino-3-(2-trifluoromethoxy)phenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate, or ethyl-
1-(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate.

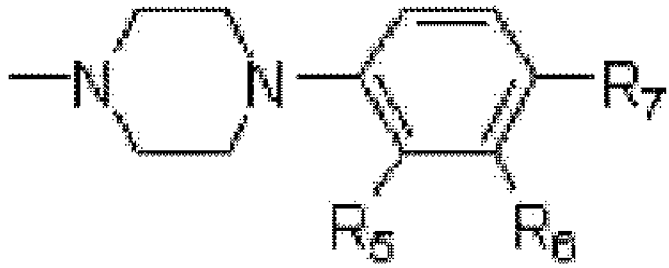
[Claim 7] The compound or itspharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, as claimed in any one of claims 1 to 5, wherein the compound comprises
(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(2-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(3-(2-chlorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,

(4-(3,4-dichlorophenyl)piperazine-1-yl)(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)methanone,
(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(4-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(3-(2-fluorophenyl)-5-methylisoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(2-hydroxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)methanone,
(4-(3,4-dichlorophenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(4-(3-methoxyphenyl)piperazine-1-yl)(5-methyl-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-chlorophenyl)isoxazol-4-yl)(4-(2-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-fluorophenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-fluorophenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(3,4-dichlorophenyl)piperazine-1-yl)methanone,

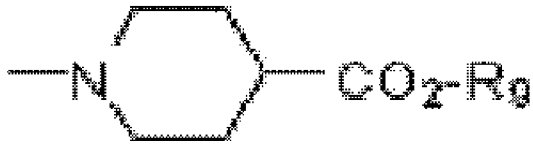
(5-amino-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(2-trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3,4-dichlorophenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(3-methoxyphenyl)piperazine-1-yl)methanone,
(5-amino-3-(3-(trifluoromethoxy)phenyl)isoxazol-4-yl)(4-(2-hydroxyphenyl)piperazine-1-yl)methanone, ethyl-1-(5-amino-3-(2-chlorophenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate, or ethyl-1-(5-amino-3-(2-trifluoromethoxy)phenyl)isoxazol-4-carbonyl)piperidine-4-carboxylate.

[Claim 8] A method for preparing the compound represented by Formula 1, as claimed in claim 1, the method comprising the steps of:
reacting a compound represented by Formula 4 below with hydroxylammoniumchloridein the presence of a base to produce a compound represented by Formula 5 below;
chlorinating the compound represented by Formula 5 so as to produce a compound represented by Formula 6 below;
cyclizing the compound represented by Formula 6 so as to produce a compound represented by Formula 7 below as an isoxazol compound;
removing R_{10} as an alkyl group of Formula 7 so as to produce a compound represented by Formula 8; and
reacting the compound represented by Formula 8 with a compound represented by Formula 2 or Formula 3 so as to produce a compound represented by Formula 9a or Formula 9b:

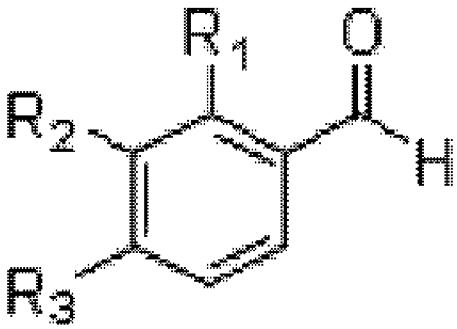
Formula 2



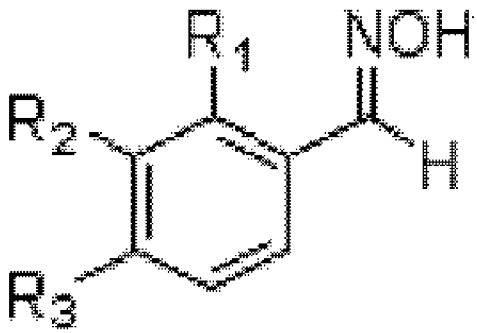
Formula 3



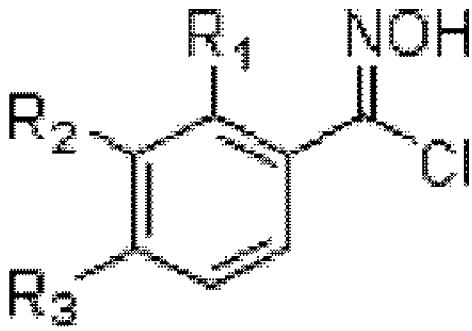
Formula 4



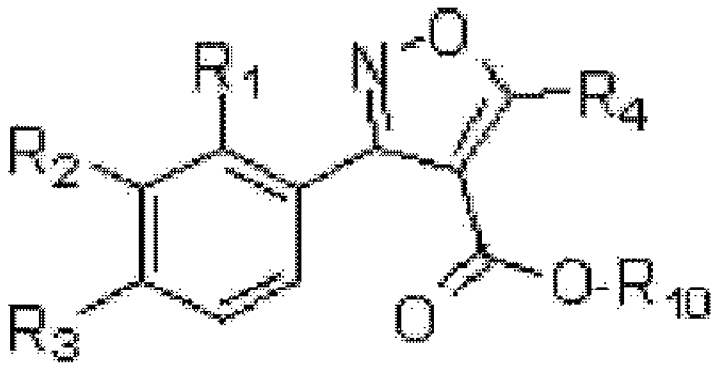
Formula 5



Formula 6

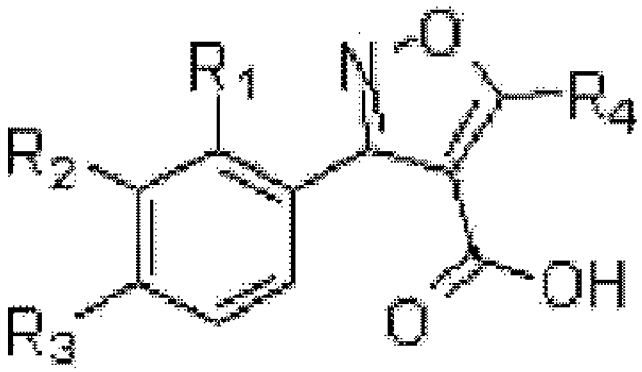


Formula

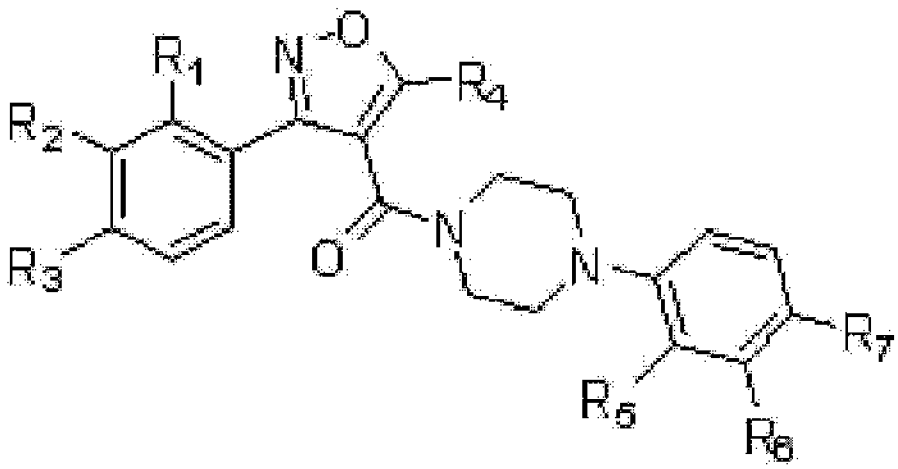


7

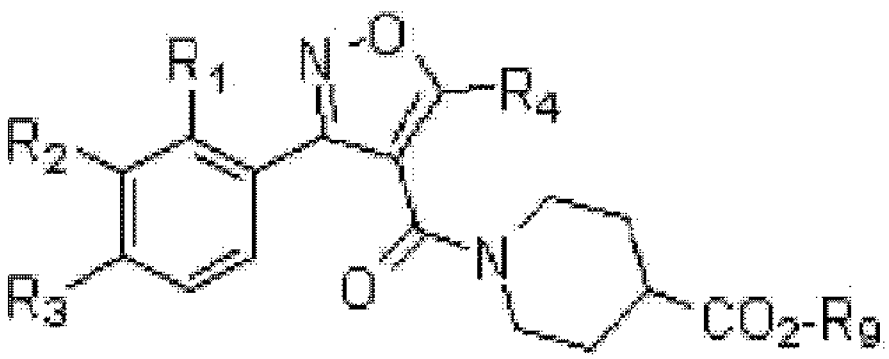
Formula 8



Formula 9a



Formula 9b



wherein in Formulas above,

R_1 to R_9 are the same as defined in claim 1, and

R_{10} represents a lower alkyl group, preferably methyl, ethyl or an isopropyl group.

[Claim 9] The method as claimed in claim 8, wherein the method is carried out in the presence of a general solvent and/or an acid or a base, in which the solvent, the acid and the base have no adverse effect on a reaction.

[Claim 10] The method as claimed in claim 9, wherein the solventis at least one kind selected from the group consisting of tetrahydrofuran, methylene chloride, ethanol, N,N-dimethylformamide, N,N-dimethylacetamide, ethylacetate, tert-butanol, toluene and dioxane.

[Claim 11] The method as claimed in claim 9, wherein the baseis at least one kind selected from the group consisting of pyridine, triethylamine, diethylamine, sodiumcarbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride, sodium methoxide, sodium ethoxide, sodium t-butoxide, potassium t-butoxide, lithium aluminum hydride, lithium borohydride, sodium nitrate and cesium carbonate.

[Claim 12] The method as claimed in claim 9, wherein the acid is at least one kind selected from the group consisting of trifluoroacetic acid, hydrochloric acid, nitric acid, sulfuric acid, bromic acid, zinc bromide and acetic acid.

[Claim 13] A composition comprising the compoundas claimed in any one of claims 1 to 6, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, and its pharmaceutically acceptable carrier or excipient.

[Claim 14] A pharmaceutical compositionfor treating or preventing virus infection, the pharmaceutical composition comprising the compound as claimed in any one of claims 1 to 6, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, and its pharmaceutically acceptable carrier or excipient.

[Claim 15] A combination comprising the compound as claimed in any one of claims 1 to 6, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, together with another virus infection therapeutic or preventive agent such as Zanamivir, Oseltamivir, Amantadine or Rimantadine.

[Claim 16] Use of the compoundas claimed in any one of claims 1 to 6, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, for preparing a pharmaceutical compositionfor treatment or prevention

of virus infection.

[Claim 17] A method for preventing or treating virus infection, comprising administering a therapeutically effective amount of the compound as claimed in any one of claims 1 to 6, or its pharmaceutically acceptable salt, hydrate, solvate, prodrug, or composite, to mammals, including humans, requiring virus infection treatment or prevention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2012/002362

A. CLASSIFICATION OF SUBJECT MATTER

C07D 413/06(2006.01)i, A61K 31/496(2006.01)i, A61P 31/16(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 413/06; C07D 413/12; C07D 295/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011-015037 A1 (THE UNIVERSITY OF HONGKONG) 10 February 2011 See pp. 39-43.	1-16
X	SU, C.-Y. et al., "High-throughput identification of compounds targeting influenza RNA-dependent RNA polymerase activity", Proceedings of the National Academy of Sciences of the United States of America (2010), Vol. 107, No. 45, pp. 19151-19156, ISSN: 0027-8424 See table 1.	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 SEPTEMBER 2012 (24.09.2012)	**24 SEPTEMBER 2012 (24.09.2012)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
LEE, Dong Wook
Telephone No. 82-42-481-8163

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2012/002362

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 17 pertains to a method for treatment of the human by therapy, and thus relates to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2012/002362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011-015037 A1	10.02.2011	CA 2770140 A1	10.02.2011
		KR 10-2012-0092567 A	21.08.2012